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**14. ABSTRACT**

Three areas emerged where the PTSD/mTBI participants showed strengths in executive control functions: (1) overriding conflicting response cues in a flanker task, (2) overcoming proactive interference in working memory (suppressing material that is no longer relevant), and (3) stopping a motor response that was already planned. These strengths are closely related to other executive functions that were weaker in the PTSD/mTBI participants. They showed pronounced deficits in (1) motor response inhibition, (2) consistency in responding, and (3) control over emotional reactions to trauma reminders. Although they were not uniformly impaired in multitasking, the patients showed behavioral and electrophysiological deficits in working memory retrieval that became apparent only when they performed a secondary task during the delay interval. Ultimately, these types of dissociations are informative for demonstrating that PTSD/mTBI can spare some important cognitive abilities. These strengths could be exploited in future developments of psychotherapy and cognitive rehabilitation techniques.

**15. SUBJECT TERMS**
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## Table of Contents

INTRODUCTION: Combat veterans who have sustained a traumatic brain injury (TBI) can show impairments in behavioral and cognitive control and increases in impulsivity. In addition, many with mild TBI will also have post-traumatic stress disorder (PTSD). To improve diagnostic capabilities and better define treatment alternatives, it is important to determine the unique (and shared) contributions of each disorder to deficits in cognitive function and emotional control. Three specific control functions are being targeted: (1) **resolving conflict** between competing responses and competing aspects of a visual display; (2) **monitoring for errors** in performance and adjusting behavior accordingly; (3) **multi-tasking**, or the ability to maintain adequate performance in dual task situations. Converging evidence is obtained through the combined use of behavioral testing, electrophysiological recording (event-related potentials, ERPs), and structural imaging (diffusion tensor imaging, DTI). The project applies innovative methods by expanding the application of ERPs into the cognitive and behavioral domains most troublesome for patients with TBI and PTSD.

BODY: The research accomplishments associated with each task outlined in the approved Statement of Work are summarized below.

| **Project Timeline and Milestones** | | | | | |
|---|---|---|---|---|---|
| | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **totals** |
| **Patient Recruitment** | | | | | |
| **Civilian Controls** | 1 | 10 | 14 | 6 | 31 (3) |
| **Military Controls** | 3 | 15 | 12 | 6 | 34 (2) |
| **mTBI Patients** | 0 | 1 | 0 | 2 | 3 (1) |
| **PTSD Patients** | 4 | 4 | 0 | 3 | 11 (1) |
| **mTBI + PTSD** | 13 | 9 | 4 | 8 | 34 (3) |
| **Pilot Studies** | Exp. 1-2 | Exp. 4 | Exp. 4 | Exp. 3 | |
| **Behavioral Testing** | Exp. 1 | Exp. 1 | Exp. 1 | Exp. 1 | |
| **ERP Testing** | | Exp. 2 | Exps. 2, 4 | Exp. 3, 4 | |
| **Integrative Analysis** | | ongoing | ongoing | completed | |

Note: In the **totals** column, the number in parentheses indicates the number of individuals who had to be excluded after enrollment, once an exclusionary criterion was discovered. They are ***not*** included in the "total" figure to the left.

**Phase 1: Patient Recruitment:**

Over the four years of the project, we recruited 31 civilian controls, 34 military controls, and 48 patients. Of the patients, there were 3 mTBI only, 11 PTSD only, and 34 with mTBI + PTSD. Not included in these totals were 10 individuals excluded after enrollment. This number included 3 civilian controls (2 with probable mTBI, 1 bipolar disorder), 2 military controls (1 with probable TBI, 1 "other" psychiatric), and 5 patients (1 potential mTBI-only patient actually had moderate TBI; 2 patients were not OEF/OIF; 1 patient had childhood TBI; and 1 patient had other medical issues).

Our original goal was to recruit 40 participants in each of the three patient groups. We came closest to meeting this goal for the combined mTBI + PTSD group. We were unsuccessful in recruiting a cohort of mTBI patients without PTSD. This issue has affected all investigators working with similar groups of OIF/OEF Veterans, and the high level of co-morbidity became

more apparent over the course of the project. Over four years, our observations were that most of the patients who meet the selection criteria for mTBI also have a formal PTSD diagnosis. Therefore, it was necessary to drop this group from the project. In our experience, these individuals might show better recovery from post-concussive symptoms (PCS) and hence do not show up at neurology or mental health clinics, or else they may not receive their health care from the VA. We tried many different avenues for recruitment and even applied for funding to recruit a cohort of athletes with concussions.

Nonetheless, we were able to make meaningful comparisons between the mTBI + PTSD and PTSD-only groups in some of the studies, as outlined in Phase 3 below. Our results agree with an increasing number of studies revealing that PTSD makes a substantial contribution to the persistent PCS and cognitive problems reported by OEF/OIF Veterans (Hoge et al., 2008; Lippa et al., 2010; Polusny et al., 2011).

**Phase 2: Pilot Studies:**

(A) Allocation of Attention: As part of our regular EEG protocol, all subjects performed a brief auditory "oddball" task containing many frequent or **standard** trials, along with occasional infrequent **targets** that required a response. The infrequent targets elicit a large positive ERP waveform over the central-parietal brain regions, commonly referred to as the P300 or P3b (Polich, 2007). A third stimulus type was also included: a **novel** non-target stimulus. No behavioral response was required to the novel stimulus, which elicits the P3a component over frontal brain regions (Knight, 1984). Previous work has demonstrated that PTSD patients show an enhanced P3a response to novel stimuli in the three-stimulus auditory oddball (Kimble et al., 2000). This is consistent with the theory that PTSD patients are more affected by distracting, unusual stimuli, which may lead to difficulties in concentration. Based on the existing literature, we predicted that participants with PTSD would show an enhanced P3a novelty effect.

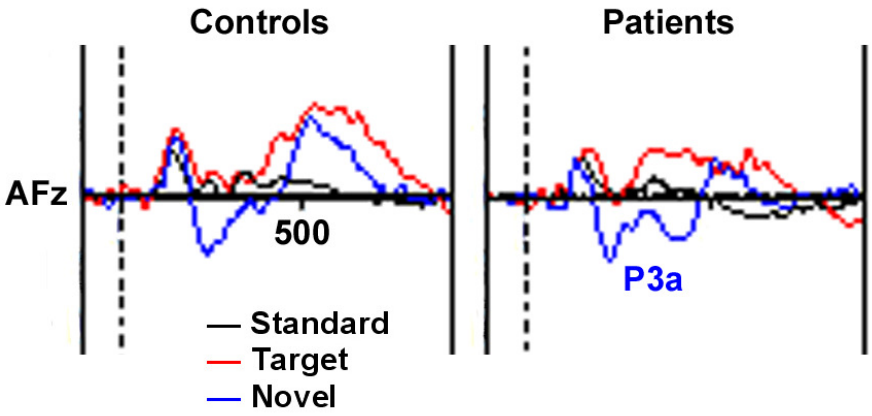


**Fig. 1** – Event-Related Ps in the auditory oddball task. Averaged ERPs from controls (n=11) and patients with both PTSD and mTBI (n=11). The standard stimulus was a 1000 Hz tone, the target a 1200 Hz tone, and the novels were unique sound effects (e.g., car horn, waterfall, machine noises) that did not repeat from trial to trial. The midline anterior frontal electrode (AFz) highlights the P3a component (in blue). Negative polarity is plotted upwards, stimulus onset occurred at the zero line.

Preliminary results from 11 controls and 11 patients with both PTSD and mild TBI are shown in Fig. 1. As predicted, the patient group showed an increase in the overall mean amplitude of the P3a, consistent with their PTSD diagnosis. The patients also showed a delay in the peak latency

of the P3a component, suggesting it took them longer to fully evaluate the novel stimuli.

(B) Support Vector Machine Classification: One of the goals of examining neural activity in patients with mTBI and PTSD is to gain a better understanding of the cognitive deficits seen in individuals with these disorders. These characterizations might also make it possible, using only electrophysiological data, to classify individuals as either having the disorder or as not having indicators of the disorder. This has the possibility of aiding health care professionals in assessing the extent and nature of the neural alterations resulting in one or more disorders. One way of doing this is through machine learning. Support vector machines (SVMs) are supervised learning methods used for classification, regression, novelty detection, and pattern recognition (Karatzoglou et al., 2006).

Devin Adair, a student in the lab, began to apply this type of analysis to the novelty P3a data (Adair, 2011). The data were filtered from 2-30 Hz and the area under the curve was measured from 250 to 300 msec. SVM analysis was done in R using C-Classification. Although the results are extremely preliminary at this point, classification of groups resulted in above chance (50%) mean classification for each group (PTSD/mTBI and Military Controls) and overall percent correct for the P3a (% Correct=64.19, $p<0.0001$; PTSD/mTBI %=61.2, $p<0.0001$; Military Control %=66.86, $p<0.0001$).

Although these percentages are not very impressive yet, improvements to the signal/noise ratio, an increase in the number of subjects, and inclusion of more variables in the model may help in the future to improve the % correct classification based on EEG measures. Georgopoulos and colleagues (2010) have been successful in using this approach with magnetoencephalographic (MEG) data, but the required equipment is expensive and rare. EEG can potentially provide a much more accessible approach.

(C) Structural MRI: Progress in collecting structural MRI data was hampered by the fact that the 1.5 T Phillips scanner at Martinez was taken out of service on approximately half way through the project and replaced with a 3 T Siemens Verio scanner. Developing new pulse sequences and establishing other research protocols took a number of months, so the new scanner was not operational until recently. However, structural MRI data from 8 patients and 8 controls were obtained with the 1.5 T scanner by our colleagues, research neuroimaging director Dr. David Woods, physicist Dr. XJ Kang, and statistician Timothy Heron. Unfortunately, we were not able to do structure/function correlations with this low *n*, but preliminary pilot data are presented below. This initial phase applied multimodal surface-based morphometry to precisely measure the area, thickness, and tissue properties of the anterior cingulate gyrus, a region implicated in error monitoring (see Exp. 2). No differences between groups in were observed in midline cingulate regions (Fig. 2, next page).

DTI studies thus far have yielded mixed results in veterans with mTBI due to blast. One report failed to detect differences in the brains of OEF/OIF Veterans with mild to moderate TBI (Levin et al., 2010). Another study in military personnel with more "severe" mTBIs (from a combination of blast injury and secondary head trauma), i.e., the group of U.S. military personnel airlifted to Landstuhl Medical Center in Germany, did show evidence of white matter abnormalities on DTI scans (Mac Donald et al., 2011). However, a new paper by Bazarian et al. (2012) found that DTI measures were not related to mTBI diagnosis in a group of 52 OEF/OIF Veterans. Therefore, it is important to pursue research with other imaging modalities to find reliable biomarkers of blast injury.

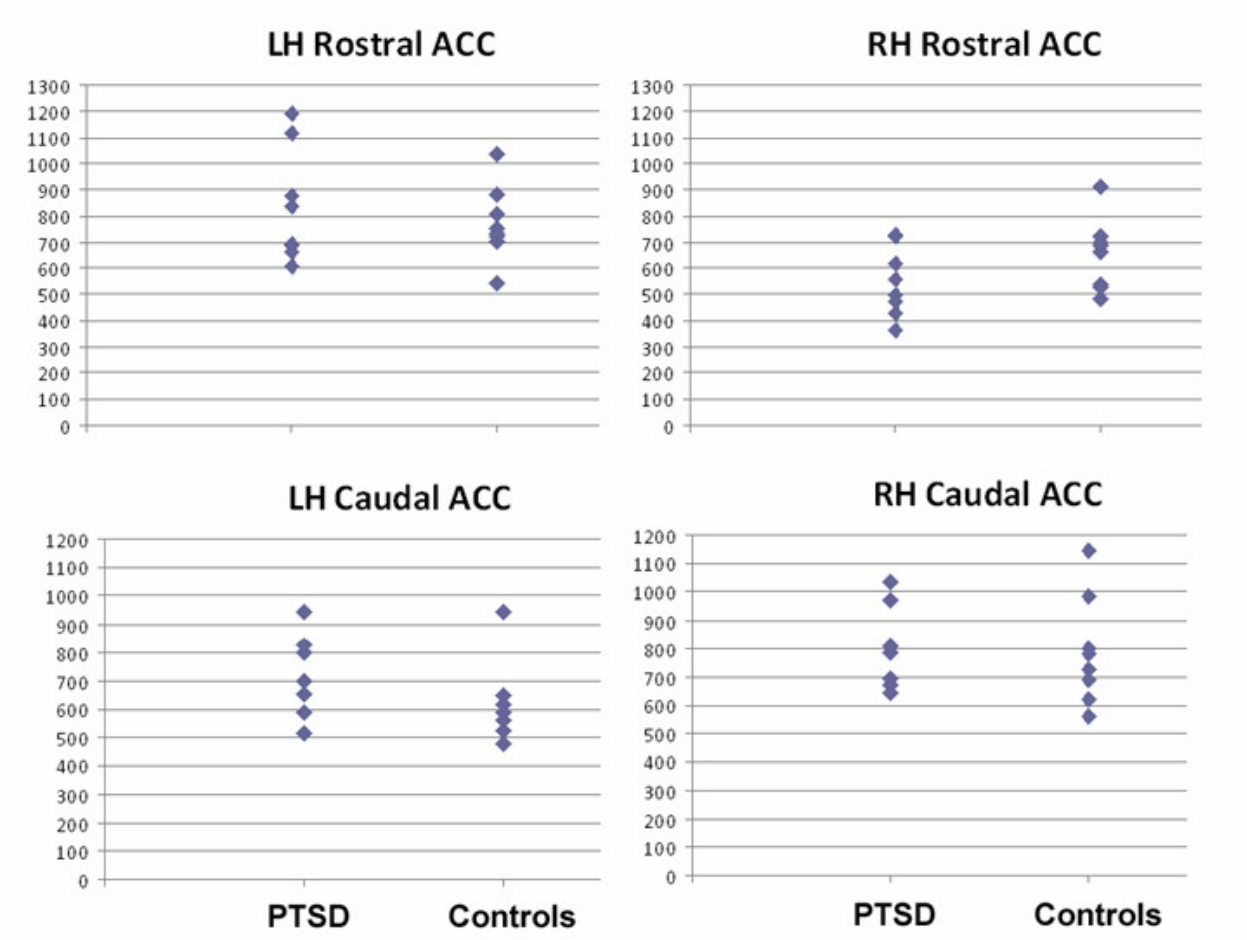


**Fig. 2** – Surface-Based Multimodal Morphometry. Area measurements from the rostral and caudal anterior cingulate cortices of patients with PTSD and age-matched military control participants. LH = left hemisphere, RH = right hemisphere.

## Phase 3: Behavioral Testing:

Three publications have resulted from this phase of the project thus far, with others in preparation. A manuscript describing results from the emotional Stroop task (Exp. 1) is attached as Appendix 1 (Ashley et al., pending revision). Results from the Go/NoGo (GNG) task, another executive control task that provides a measure of response inhibition, have been published (Swick et al., 2012; Appendix 2). A third paper provides a meta-analysis of brain regions activated during performance of the GNG and another response inhibition task (Swick et al., 2011a; Appendix 3). Brief summaries are provided below, along with detailed results from related studies. Abstracts from conferences are included as Appendices where appropriate.

(A) Experiment 1: Emotional Stroop task with Combat-Related Words (Appendix 1):

This experiment was designed to be an objective behavioral measure that may be able to distinguish between combat Veterans with a PTSD diagnosis and those without. The participants were 30 PTSD patients, 30 military controls, and 30 civilian controls. Words were presented in blocks of negative emotional words, positive emotional words, combat-related words (specific to OEF/OIF), and appropriately matched neutral words. The metric of interest was the emotional Stroop effect, or slowing of reaction times (RTs) for naming the color of combat words relative

to neutral words. Trauma-relevant material is thought to divert attention away from the primary task in those with PTSD. The emotional Stroop effect was nearly three times larger in the patient group (112 msec) than that seen in the military control participants (41 msec). There were also significant correlations between the size of the combat Stroop effect and scores on the PTSD Checklist-Military (PCL-M). Thus, the emotional Stroop task shows promise as an objective indicator of PTSD symptomology suitable for use as an outcome measure in PTSD intervention studies (Ashley et al., pending revision). We have made our stimulus list available as an Appendix of the manuscript, which will appear in the article when it is published. In fact, we have already been contacted by other investigators who wish to use our stimulus list in their treatment studies, as a pre-/post-treatment measure of efficacy in lowering attentional bias to trauma reminders in the OEF/OIF veteran population.

(B) Go/NoGo Task – Motor Response Inhibition (Appendix 2):

This task measures a person's ability to inhibit an inappropriate response. Single letters were rapidly presented on a computer screen, and subjects were instructed to respond as quickly as possible to any letter except "X," the NoGo stimulus. The difficulty of the task was manipulated by altering the probability of "NoGo" trials relative to "Go" trials, i.e., 50% NoGo (easy) vs. 10% NoGo (hard). Performance measures from the patient group (n=40) were compared to those from an age-matched Veteran control group (n=33). The patients were significantly impaired on this task overall, committing more errors in both conditions ($p<.0001$). Furthermore, "Go" probability interacted with group ($p<.003$), reflecting an exacerbated deficit in the hard condition. Veterans with mTBI+PTSD did not make more mistakes on this task than Veterans with PTSD only, suggesting that an additional mTBI(s) did not compound the response inhibition deficit associated with PTSD (Swick et al., 2012).

(C) Response Variability (Swick et al., in preparation):

Another aspect of executive functioning is control over response variability. Consistency in behavioral responding is required for the efficient performance of many cognitive tasks. Often measured as trial-to-trial variability in RT, intra-individual variability indexes the stability of executive control processes over time (West et al., 2002). A high level of response variability has been characterized as a marker of executive dysfunction and inhibitory inefficiency, cognitive instability, and mental noise. Specific regions of the prefrontal cortex (PFC) have been associated with this aspect of cognitive control (Stuss et al., 2003). Here, the RT variability seen in the GNG task was analyzed for 34 controls and 45 PTSD patients (Swick et al., in preparation).

A measure of RT variability on Go trials, the intra-individual coefficient of variation (ICV), was obtained from the formula, Standard Deviation/mean RT (Stuss et al., 2003). The ICV ratio is a standard measure designed to correct for differences in group RTs. Statistical analysis indicated that the patients showed greater response variability than controls [$F(1,77)=12.38$, $p=.0007$]. RTs were more variable in the 90/10 condition than the 50/50 condition for all participants ($p<.0001$). Furthermore, condition interacted with group [$F(1,77)=7.27$, $p=.007$], suggesting that the patients were disproportionately impaired in the difficult 90/10 condition. Because raw RTs did not differ between the groups (controls: 379 msec and patients: 370 msec, $p=.6$), a secondary ANOVA entered SD values instead of the ratio. A main effect of group was still observed [$F(1,77)=6.12$, $p=.02$], with patients more variable than controls (95 msec vs. 73 msec). Next, the relationship between RT variability and error rate was examined. The correlation between response variability and false alarm errors was significant for both the 50/50 ($r=.56$, $p<.0001$) and the

90/10 conditions (r=.49, p<.0001), suggesting that more variable RTs were associated with a greater propensity for impulsive errors.

Despite having mean RTs that were indistinguishable from controls, the patients had greater variability in their response times. More variable RTs were in turn associated with a greater number of errors, replicating previous findings (Bellgrove et al., 2004). Increased response variability has also been observed in children with ADHD (Suskauer et al., 2008), and is viewed as another facet of their response inhibition impairments. Stuss et al. (2003) has suggested that an alteration in the consistency of task performance could contribute to the PFC patients' difficulties in everyday life. Likewise, the combination of inconsistent performance and impaired response inhibition shown by the veterans with PTSD/mTBI could have deleterious effects on daily activities requiring these cognitive control functions, such as driving (Lew et al., 2010) and multi-tasking (see Phase 4, Part C below).

(D) Stop-Signal Reaction Time Task – Motor Response Inhibition:

The Stop-Signal Task (SST) also measures a person's ability to inhibit an inappropriate response, similar to the Go/NoGo task described above. In the SST, responses are made on every trial unless a Stop Signal (e.g., a tone) is presented. The interval between the Go stimulus and the Stop stimulus (stop-signal delay) is varied using an adaptive procedure designed to produce a 50% error rate (Verbruggen & Logan, 2008). Performance is modeled as a "race" between Go and Stop processes, and the stop-signal reaction time ("stopping time") is calculated as a measure of inhibitory control.

We implemented a standard version of the task where left and right arrows are presented on the screen, each requiring a left or right key press response unless a tone is presented (25% of the trials). The Stop-Signal RT (SSRT) is a measure of the time required to cancel a movement that is already planned. More efficient stopping ability is represented by **shorter** SSRTs. Below we summarize data from 26 patients and 20 veteran controls. Statistical results indicated that stopping times (SSRTs) did not differ between the groups: 199 msec for controls and 210 msec for patients (p=.42). Thus, the ability to stop a pre-planned response is intact in these OEF/OIF veterans with PTSD. This stands in contrast with the patients' impaired performance on the GNG task. The raw RTs and error rates for SST did not differ between groups. Furthermore, patients with mTBI+PTSD (n=19) did not differ from those with PTSD only (n=7) on any measure. Next, we examined whether performance on the two tasks was correlated. NoGo errors were not correlated with Stop Signal RTs (r= -.015 for 90/10 errors, r= -.187 for 50/50 errors), suggesting the two tasks are different measures of response inhibition (Swick et al., 2011b; Appendix 11). This replicates findings reported in a large group of control participants (Aichert et al., 2012). Combined with a review of the neuroimaging literature (see section E below), these data suggest GNG and SST reflect different aspects of response inhibition.

Although these two tasks are often treated interchangeably (Lenartowicz et al., 2010), it is unclear whether they tap the same cognitive processes and neural substrates. This is important because assertions that GNG and SST are both measuring the same cognitive construct might have clinical implications. Impaired performance on either of these tasks in patient populations is often taken as an indication of specific prefrontal cortex abnormalities (Clark et al., 2007) or frontal lobe dysfunction more generally (Barkley et al., 1992). Defining the behavioral details and neural substrates of impulse control problems is an important goal for developing treatment strategies for the OEF/OIF population.

(E) Neural Correlates of Response Inhibition in GNG and SST (Appendix 3):

The discrepancies in task performance shown by the PTSD/mTBI patients are consistent with our recent discovery that GNG and SST differentially recruit two distinct cognitive control networks (Swick et al., 2011a). We conducted a meta-analysis of the neuroimaging literature to determine the brain regions that are most commonly activated by GNG and SST. Differences between the tasks were observed in two major cognitive control networks: (1) the **fronto-parietal network** that mediates adaptive online control, and (2) the **cingulo-opercular network** implicated in maintaining task set (Dosenbach et al., 2007) and responding to salient stimuli (Seeley et al., 2007). GNG engaged the fronto-parietal control network to a greater extent than SST, with prominent foci located in the right middle frontal gyrus and right inferior parietal lobule. Conversely, SST engaged the cingulo-opercular control network to a greater extent, with more pronounced activations in left anterior insula and bilateral thalamus.

Combining the neuroimaging and behavioral results, one possible interpretation is that the **fronto-parietal attentional control network** might be compromised in the patients, which led to a response inhibition deficit in the GNG task. This idea is speculative and needs to be tested more directly in an fMRI experiment. Falconer and colleagues (2008) did exactly that by administering a 75/25 Go/NoGo task to PTSD patients and controls in the scanner. The patients made significantly more errors than controls. The NoGo-Go contrast revealed that controls activated bilateral ventrolateral PFC, R orbitofrontal, R parietal and dorsal anterior cingulate. The patients showed increased activation on NoGo trials in left ventrolateral PFC and right inferior/middle temporal cortex, but not in the right hemisphere fronto-parietal network.

Another speculative observation is that **portions of the cingulo-opercular salience network** – uniquely engaged by SST (left anterior insula, thalamus) – might be less affected by mTBI and PTSD, based on intact performance in this task. The patients were similar to controls in their abilities to stop a planned response when they heard the stop-signal tone, unlike their greater difficulty with inhibiting responses to the "X" NoGo stimuli. Why might this be? One model of response inhibition (Schachar et al., 2007) distinguishes between action restraint – inhibition of a motor response before the response has been initiated (GNG), and action cancellation – inhibition of an already initiated motor response (SST). We feel that these types of studies can more precisely clarify the cognitive and attentional control networks that are affected by PTSD and mTBI, and which are intact.

(F) Impaired identification of facial expressions of fear in Iraq war veterans with PTSD and mTBI (Appendix 12): Ashley, Larsen, Pratt, & Swick, 2012 Cog Neurosci Society Meeting.

In this study, we attempted to replicate the findings of Poljac et al. (2011), who found accuracy impairments and decreased sensitivity in recognizing expressions of fear and sadness in war veterans with PTSD. We also predicted that PTSD patients would interpret ambiguous expressions as angry due to the hypervigilance for threats that is characteristic of PTSD. We expected that all subjects would make classic misattribution errors, such as mistaking Surprise for Fear, and Anger for Disgust. Initial results suggested a reduced ability to recognize lower intensity fearful expressions in the patients, but no effect on recognizing sadness (Appendix 12). However, this result was no longer significant when additional subjects were recruited (18 PTSD patients, 21 Controls). Instead, results were generally consistent with the hypothesis that PTSD patients were more likely to misattribute ambiguous expressions as Anger, and to display higher accuracy on Anger faces (perhaps due to an Anger bias).

**Phase 4: ERP Studies:**

Two publications have resulted from this phase of the project thus far, with others in preparation. A manuscript describing results from civilian control participants in the dual task/flanker study (Exp. 4) is attached as Appendix 4 (Pratt et al., 2011). Also included as Appendix 5 is a manuscript on the dual task/working memory study (another aspect of Exp. 4), with results from PTSD/mTBI patients and military controls (Honzel et al., submitted). Findings from the other experiments are also discussed below.

(A) Experiment 2 – Error Monitoring

The error-related negativity (ERN) is an ERP component generated when subjects make errors in speeded reaction time tasks (Gehring et al., 1993). This component is considered to be an on-line index of performance monitoring that reflects neural activity in the medial prefrontal cortex. Lesion evidence suggests that a major generator of the ERN is located in the dorsal anterior cingulate cortex (Swick & Turken, 2002). Initially, we reported that PTSD patients and controls showed a significant reduction in ERN amplitude, but this was no longer the case after additional subjects were run. One issue was that several of the participants performed the task incorrectly on some of the trials due to a misinterpretation of the instructions, but didn't realize it. This would negate ERN generation on those trials, because awareness of error is a crucial part of the neurophysiological response.

Fig. 3 shows the averaged ERPs from 10 controls and 10 participants with PTSD±mTBI on incorrect trials in a choice RT task. The amplitude of the ERN tended to be smaller in the patients at central and posterior electrodes, but this difference did not reach significance.

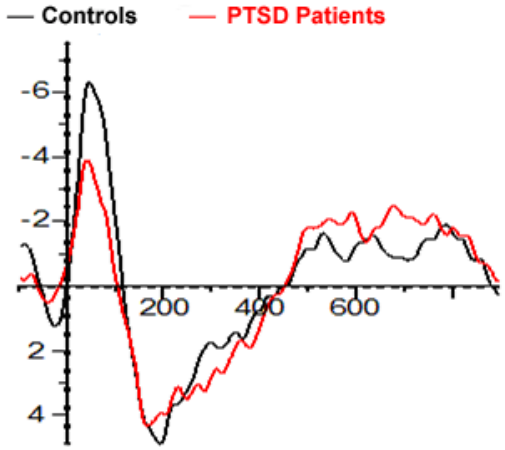


**Fig. 3** – The error-related negativity (ERN) component on error trials. ERPs recorded from a subset of controls (n=10) and patients (n=10) who correctly performed the task. These ERPs (from central midline electrode Cz) were time-locked to response onset (at the vertical marker). Negative is plotted upwards.

Prior experiments with TBI patients have focused on those with severe injuries, and these studies have reported large ERN decreases (Larson et al., 2007; Turken & Swick, 2008). The present results also differ from the enhanced ERN responses observed in populations with other anxiety disorders (generalized anxiety disorder, OCD). It is possible that mTBI and PTSD are acting in opposition, and that depression plays a moderating role. A precedent for this was observed in a recent paper by Weinberg et al. (2012). Relative to controls, ERN was increased in participants with generalized anxiety disorder, but not in those with co-morbid anxiety and major depression. The relationship between mTBI, PTSD, depression, and ACC function is complicated. In the future, studies that combine ERPs and MRI in larger groups of patients will be informative, and this is an area of research that Dr. Honzel (Pratt) wishes to pursue.

(B) Experiment 4 – Dual Task Performance in the Flanker Task:

**Background:** This study examined the effects of multi-tasking on behavioral performance and

brain activity during a selective attention task. Working memory and attention interact in a way that allows us to focus on relevant items and maintain current goals. Multi-tasking increases the demands on working memory and reduces the amount of resources available for cognitive control functions. If veterans with PTSD/mTBI have to rely on the recruitment of cognitive resources to a greater extent than controls, then their performance may suffer disproportionately while multi-tasking. Published results from civilian controls are presented in Appendix 4 (Pratt et al., 2011).

**Design:** The experimental design is a modification of that study, as shown below in Fig. 4. The flanker interference task was performed alone (single task) or concurrently with a Sternberg working memory task (dual task). In the Sternberg task, a set of 1 or 4 consonants was presented. In the single task version, the letter(s) were to be remembered during an unfilled 8.5 second delay. In the dual task version, 9 trials of the flanker task intervened during the delay.

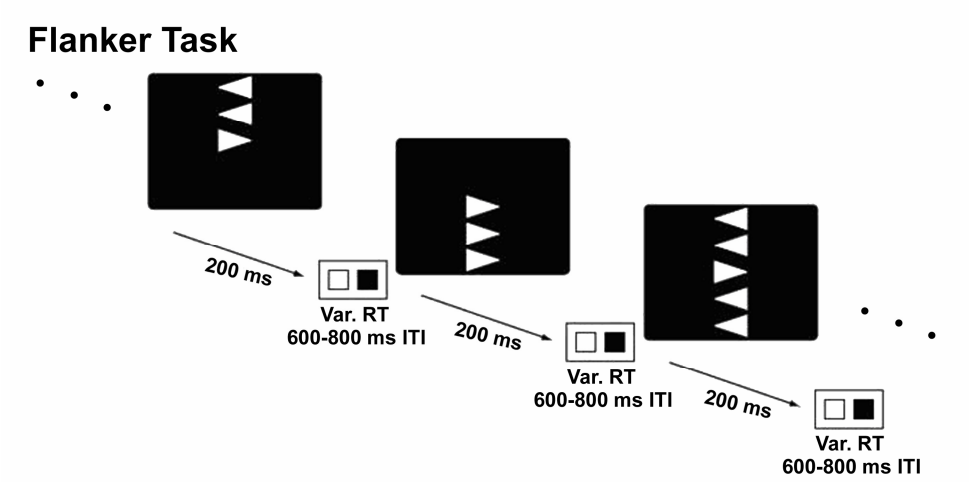


**Fig. 4** - Flanker Task Design (Honzel et al., submitted). Participants responded to direction of the central arrow using a two-button response. Flanker arrows could be either congruent or incongruent and above, below or both above and below the central arrow. In the dual task condition, participants were shown a set of 1 or 4 letters to remember at the beginning of the trial, performed the flanker task during the delay interval, then were shown a probe letter that either was or was not presented in the previous memory set.

**Behavioral Results:** In the flanker task, subjects are generally slower and less accurate on trials in which the flanker arrows are incongruent relative to the target arrow (Eriksen & Eriksen, 1974). These classic flanker interference effects were observed in the present study. All participants were 50-60 msec slower for incongruent than for congruent trials ($p<.0001$). Importantly, veterans with PTSD/mTBI performed as well as controls on both the single task and dual task versions of the flanker. This was true for both accuracy (Fig. 5, next page) and reaction times (Group x Congruence, $p=.66$).

**ERP Results:** We also recorded ERPs during both the single and dual task conditions. The P300, or late positive component (LPC), was measured as mean amplitude between 400-600 msec (Fig. 6, next page). An ANOVA with factors of Electrode (FCz, Cz, CPz, Pz), Congruence (Congruent, Incongruent), Load (Single Task, Dual Load 1, Dual Load 4), and Group yielded main effects of Congruence and Load. Across all participants, the LPC for the incongruent flanker condition was smaller than for the congruent flanker condition [$F(1,25)=8.49$, $p=0.007$] and smaller for Dual Load 4 than for the other two conditions [$F(2,50)=10.91$, $p<0.001$]. The patients and controls showed a very similar pattern of results: Group did not interact with Congruence ($p=.98$) or Load ($p=.73$).

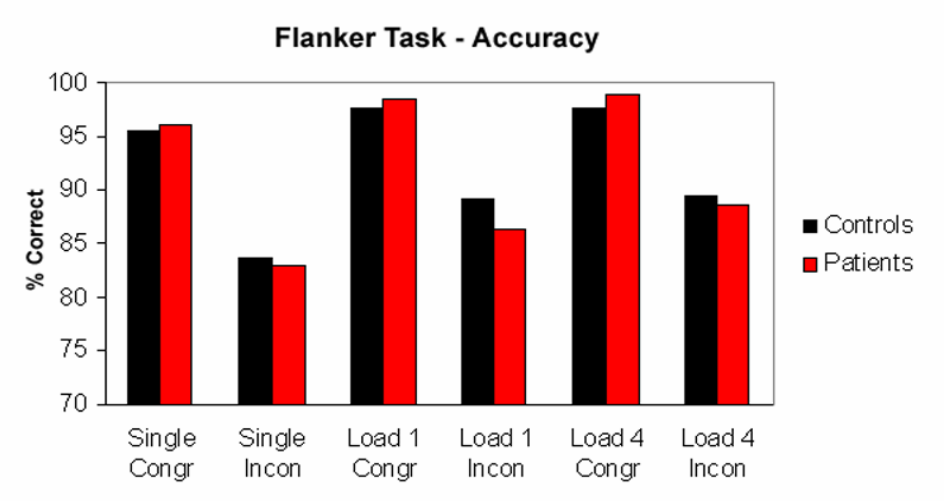


**Fig. 5** - Accuracy in the Flanker Task. Percentage of correct trials is shown for all six conditions in the PTSD/mTBI patients and matched military controls. All participants were less accurate on trials when flankers were Incongruent to the target, relative to Congruent trials. Unexpectedly, all subjects performed worse in the single task condition. However, the patients were just as accurate as controls for all conditions (p=.84). **Single Congr** = Single task flanker, Congruent trials; **Single Incon** = Single task flanker, Incongruent trials; **Load 1 Congr** = Dual task flanker, Load 1, Congruent trials; **Load 1 Incon** = Dual task flanker, Load 1, Incongruent trials; **Load 4 Congr** = Dual task flanker, Load 4, Congruent trials; **Load 4 Incon** = Dual task flanker, Load 4, Incongruent trials.

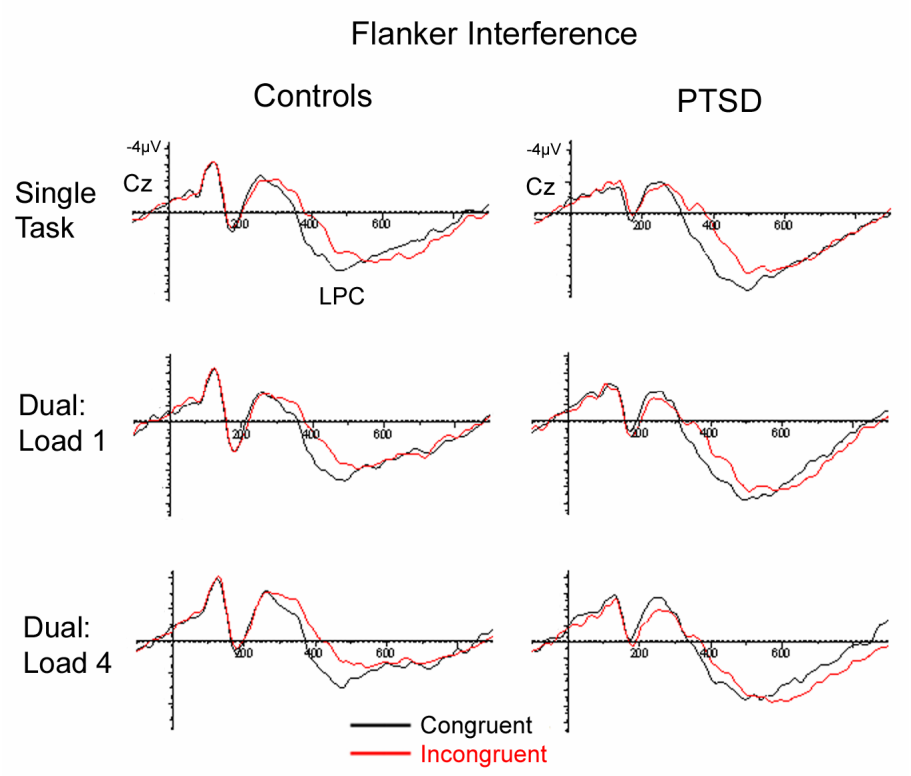


**Fig. 6** – Event-Related Potentials in the Flanker Task. ERPs recorded from 13 Control Veterans and 14 Veterans with PTSD/mTBI in the single- and dual-task flanker conditions. These ERPs (from central midline electrode Cz) were time-locked to stimulus onset (at the vertical marker). Congruent trials are in black, Incongruent trials are in red. Negative is plotted upwards. LPC = late positive component.

**Significance:** The patients' intact behavioral performance and electrophysiological responses in the flanker interference task suggest that some forms of executive control are spared in OEF/OIF veterans with PTSD/mTBI. In contrast, the PTSD patients did have problems with the working memory component of the task, especially when combined with the flanker (summarized below). This may have implications for the successful completion of everyday activities.

(C) Experiment 4 – Dual Task Performance in the Sternberg Memory Task (Appendix 5):

**Background:** The current experiment set out to determine if the working memory (WM) impairments observed in previous studies of PTSD (e.g., Bremner et al., 1993) can be linked to executive control limitations. Here we examined ERPs and behavioral performance on the Sternberg WM task alone and when the flanker interference task was performed during the maintenance period. Reduced accuracy on the WM task only under difficult conditions could suggest dysfunction in the central executive component of WM (Baddeley, 1996), rather than a general decline in remembering information across a short delay.

**Behavioral Results**: In contrast to their intact performance on the flanker task, the patients were less accurate than controls on the Sternberg working memory task, and their performance suffered to a greater extent in the dual task than in the single task version. This was supported by a main effect of Group and a Group by Task interaction. The patients showed a trend for worse performance in the single task Sternberg but were significantly less accurate than controls on the dual task Sternberg, when the demanding flanker task occurred during the working memory delay (Appendix 5, Honzel et al., submitted).

**ERP Results**: The PTSD patients showed a reduction in the electrophysiological correlate of working memory retrieval in the dual task condition only. This ERP response, the old/new effect, differentiates correctly recognized old items from correctly rejected new items, beginning at 300 msec post-stimulus and continuing for several hundred milliseconds. The ERP old/new effect was intact in the single task version of the Sternberg, suggesting that the neural processes underlying working memory retrieval were spared when distraction was minimized (Appendix 5, Honzel et al., submitted).

**Discriminant Analyses:** Based on these results, two separate discriminant analyses were performed to examine whether behavioral performance or electrophysiological recordings could predict PTSD group membership. One discriminant analysis used PCL-M scores as the dependent variable and accuracy in the dual task condition as predictor variables. The other discriminant analysis used PCL-M scores as the dependent variable and the ERP old/new effect between 300-400 msec as the predictor variable. For the accuracy analysis, the value of the discriminant function was significantly different for PTSD and controls (chi-square=5.12, p=0.024). Overall, the discriminant function successfully predicted 68.8% of cases, with accurate prediction being made for 87.5% of the controls, but only 50% of the PTSD patients. The analysis for the ERP as the predictor variable was also significantly different for PTSD patients and controls (chi-square=6.43, p=0.011). However, the discriminant function correctly classified 71.9%, with accurate predictions being made for 68.8% of controls and 75% of patients. Therefore, ERPs were better at predicting group membership than behavioral performance.

**Significance:** These findings suggest that working memory performance is compromised in OEF/OIF veterans with PTSD/mTBI when additional cognitive demands require multi-tasking. The ERP results indicate that the addition of a secondary task during the retention interval interfered with item recognition. Conversely, performance on the secondary task was not

impaired in the patients. Responding quickly and correctly on incongruent flanker trials requires one to override automatic response tendencies. This form of executive control was intact in the PTSD/mTBI group, unlike the impairments that were seen in response inhibition (Go/NoGo task) and emotional control (emotional Stroop task). These types of dissociations are informative for theoretical models of executive control function (Miyake et al., 2000), as well as for demonstrating that PTSD/mTBI can spare some important cognitive abilities.

(D) Experiment 4 – ERP and EEG Spectral Analyses During Memory Encoding and Retention:

Because of the behavioral and neurophysiological deficits shown by the patients during the memory retrieval phase, it is important to determine whether there are also weaknesses during the memory encoding and delay intervals. To better understand the nature of the multi-tasking problem exhibited by the patients, we conducted analyses of EEG activity during the encoding and delay period of the Sternberg memory task, considering the effects of both Set Size (i.e., whether participants are maintaining 1 letter or 4 letters in working memory) and of Task (i.e., whether participants are maintaining the letters with no distraction or performing the secondary flanker task during the delay). In addition to performing an ERP analysis time-locked to encoding, we also analyzed the data in the frequency domain on a second-by-second basis as the participants encode the stimuli to be remembered and maintain them during the delay. The focus is on EEG activity in the theta (~3-7 Hz) and alpha (~7-13 Hz) bands (e.g., Khader et al., 2010).

ERP analyses at encoding suggest interactions between Set Size, Task, and Group (p=.02). Once the array of letters to be remembered has been presented, only the individuals with PTSD demonstrate a significant effect of set size (1 vs. 4 letters), and only if the secondary flanker task is about to begin during the maintenance interval (Fig. 7). This set-size differentiation at encoding is not obtained for the PTSD patients in the single task, nor for the controls in either condition. These data might suggest that control participants are well within the capacity limits of working memory at encoding, regardless of whether the set size is 1 or 4, and regardless of whether the secondary flanker task is beginning to divert cognitive resources. Individuals with PTSD, however, may be within working memory capacity only for the single task condition, in which they can maintain the letters without additional distraction. With an impending flanker task, limited cognitive resources would seem to be diverted away from the Sternberg letters at encoding.

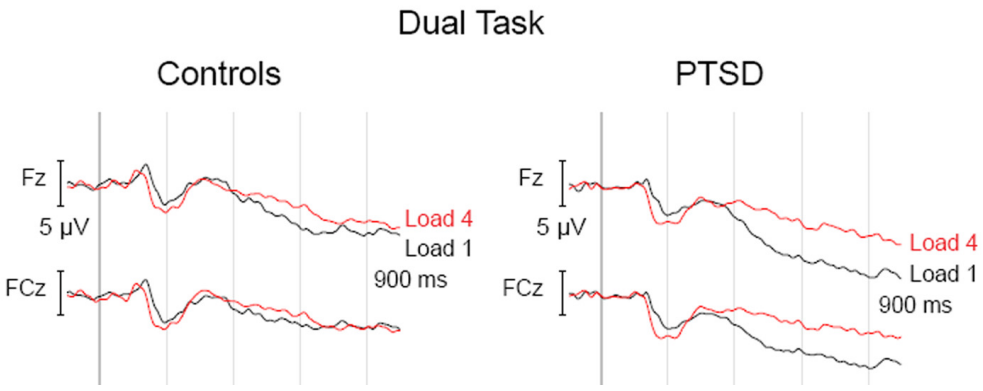


**Fig. 7** – ERPs During Encoding of the Memory Set. ERPs in the Sternberg WM task were recorded from 16 Control Veterans and 17 Veterans with PTSD/mTBI during stimulus encoding in the dual task condition. These ERPs (from frontal and frontocentral midline electrodes) were time-locked to stimulus onset (at the vertical marker). Load 1 is in black, Load 4 is in red. Negative is plotted upwards.

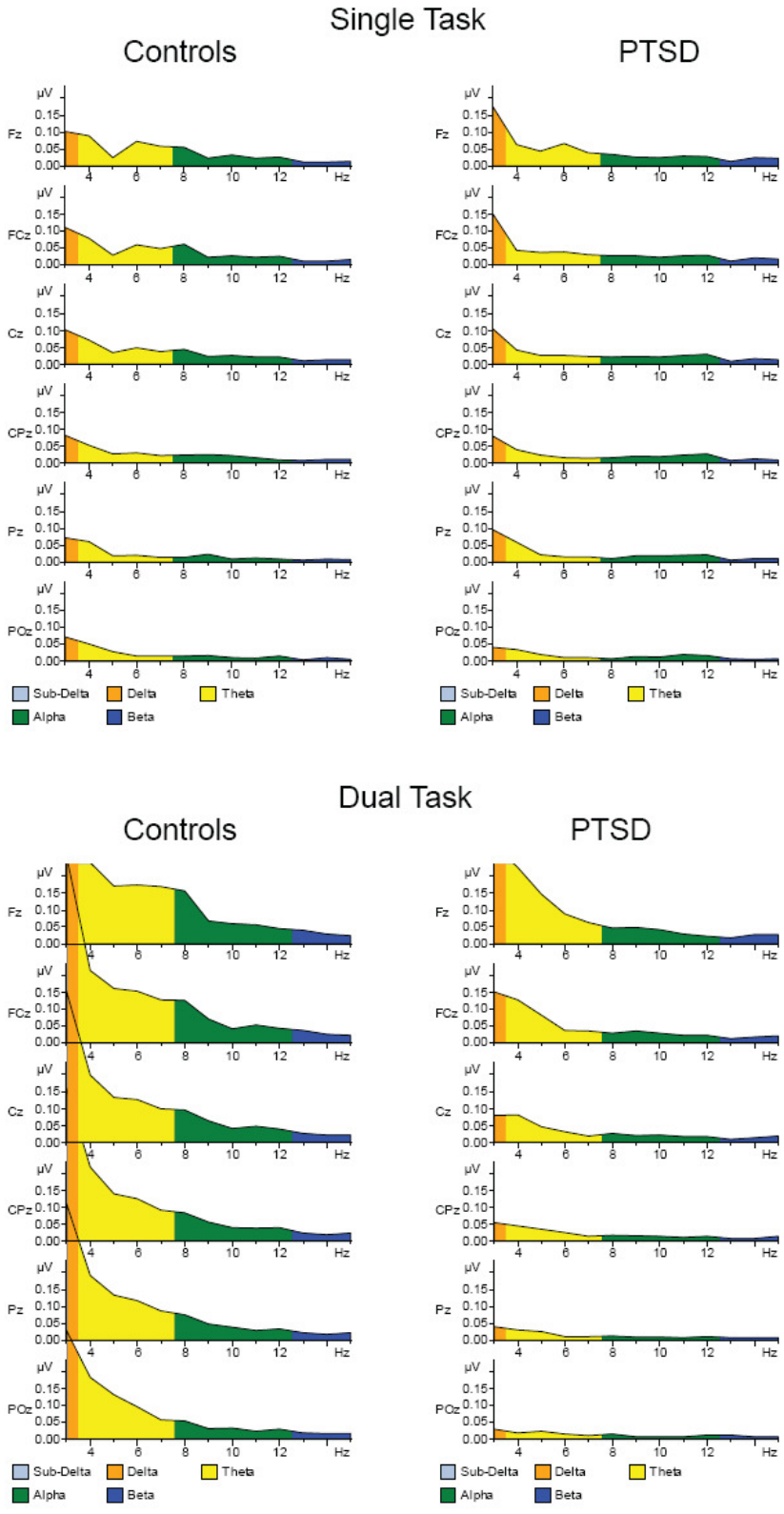


**Fig. 8** – EEG Spectral Analysis During Encoding of the Memory Set. Fast Fourier Transform was applied to the EEG data during the 1000-2000 msec post-stimulus interval, when participants were encoding the set of letters to be remembered across a short delay. Note the reduction in theta and alpha power in the PTSD patients during the dual task condition.

A preliminary frequency-domain analyses using a fast Fourier transform is suggestive of spectral differences between the controls and PTSD patients, even as the Sternberg letters are being encoded (Fig. 8, previous page). Specifically, power values in the theta and alpha bands tend to be larger in the dual-task condition than the single-task condition, and tend to be larger for control participants than the PTSD participants. These differences seem particularly prominent in a 1000-2000 msec window defined relative to the onset of the Sternberg memory set.

(E) Working Memory for Verbal and Visual Material:

**Background:** This study is a further exploration of working memory abilities in the OEF/OIF population. Other researchers have reported WM impairments in PTSD patients when non-emotional material was used (Bremner et al., 1993), and we observed a verbal WM deficit in the previous study when executive processing resources were taxed (Exp. 4). However, there is a debate as to whether verbal working memory (and verbal memory more generally) might be impaired to a greater extent than visual memory (Brewin et al., 2007).

**Design:** The experimental design adopted the item recognition task of Thompson-Schill et al. (2002), but used words and visual patterns (instead of letters) as the stimulus material. Participants were required to judge whether a test probe item was a member of a set of studied items. At the beginning of each trial, a "Get Ready" cue was presented for 1,000 msec. This was followed by a cross in the center of the screen. After 500 msec, the target set was presented. The target set was a visual display of four words or visual patterns arranged above, below, to the left, and to the right of a central fixation cross. The target set remained on the screen for 1,500 msec, followed by a 3,000-msec delay. Following this delay, the probe (i.e., a single word or pattern) appeared in the central location, and the subject was instructed to indicate whether that probe was a member of the current target set or not. Proactive interference (intrusions of previously studied, but now irrelevant stimuli) was examined as well.

**Results:** All participants were much better at remembering verbal than visual (nonverbal) stimuli ($p<.0001$), despite our efforts to match the stimulus sets for difficulty. The patients made significantly more errors than controls ($p=.01$), and this pattern was similar for both verbal and nonverbal items (Group x Stimulus Material, $p=.59$; see Fig. 9, Left). Thus, the hypothesis of selective impairment in verbal working memory was not supported.

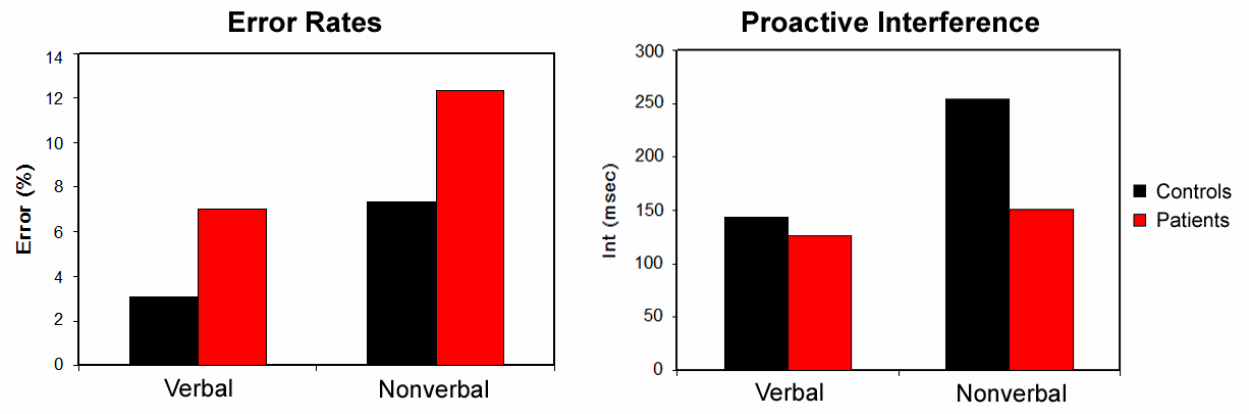


**Fig. 9** – Performance in the Working Memory Task. **Left:** Error Rates Percentage of incorrect trials for 16 Control Veterans and 18 Veterans with PTSD ± mTBI. The patients were impaired to a similar extent for both verbal and nonverbal stimuli. **Right:** Proactive Interference. RT slowing (in msec). The patients tended to show less interference from previously encoded but now irrelevant items.

Conversely, proactive interference (measured as RT slowing) was unexpectedly *lower* in the PTSD/mTBI patients (p=.07), although this was only a trend (see Fig. 9, Right). It appeared that the reduction was larger for nonverbal material, but the interaction with group was not significant (p=.12).

**Significance:** The ability to suppress proactive interference is thought to require executive control processes in the PFC (Thompson-Schill et al., 2002). The patients with PTSD were unexpectedly better at this, which could indicate either (1) Weaker encoding of the studied items led to fewer subsequent intrusions and less interference; or (2) the PTSD patients were able to better suppress stimuli that were no longer relevant, which would be an important observation for the management of flashbacks and other disturbing memories. This interpretation should be made cautiously, however, since the difference between groups was not significant. Nonetheless, future studies that use emotional and trauma-relevant material within this design would be informative.

(F) Experiment 3 – Performance Monitoring and Motivational Significance:

**Background:** Exp. 3 investigates the role of motivation and task engagement on the neural activity associated with performance monitoring and the evaluation of feedback. It also assesses the participants' propensity to engage in impulsive choices and their level of reward-sensitivity. A specific EEG component, called the feedback negativity (FN), has been interpreted as reflecting an error in reward prediction (Miltner et al., 1997; Gehring & Willoughby, 2002). The neural generator of the FN is thought to be located in the medial frontal cortex, which is involved in processing feedback signals. This study pursues the questions of whether PTSD/mTBI patients will show a normal FN response to performance feedback in a blackjack task (e.g., win or loss), and the degree to which the electrophysiological response is sensitive to reward magnitude.

**Design:** The experiment consists of computer simulated game of blackjack that is realistic, with the participant playing against a "dealer" and making decisions on whether to "stay" or "hit" (draw another card). If the player beats the dealer, they win the hand and gain a financial reward. If they lose the hand to the dealer or "bust" (go over 21), they pay a penalty. All participants start with a set sum of money with which they may gamble. To increase motivation, subjects receive the monetary earnings at the end of the game; however, participants are not required to pay if they end up in the red. EEG analyses initially focus on the responses to positive feedback (wins) and negative feedback (losses). In addition, responses to negative and positive feedback displays following high-risk choices (e.g., dealt two cards that sum 18, draw another card) are compared to those following low-risk choices (e.g., dealt two cards that sum 14, draw another card).

**Results:** Preliminary results in 15 civilian controls revealed an FN component at 300 msec that is larger to feedback indicating a loss, rather than a gain (Fig. 10). The expected results were obtained, and future studies will be conducted using this design in PTSD/mTBI patients and age-matched military controls.

**Significance:** We predict that individuals with mTBI (with or without PTSD) will show reductions in FN amplitude, specifically in relation to negative feedback following high-risk decisions. This would suggest that normal function of the orbitofrontal cortex is compromised, based on ERP findings showing error monitoring deficits in severe TBI patients (Turken & Swick, 2008), and on prior studies of impulsive choice (Dalley et al., 2011). Results from this experiment will have important implications for evaluating real-life changes that can occur after TBI, such as increases in impulsive behaviors, including addictions and problematic gambling.

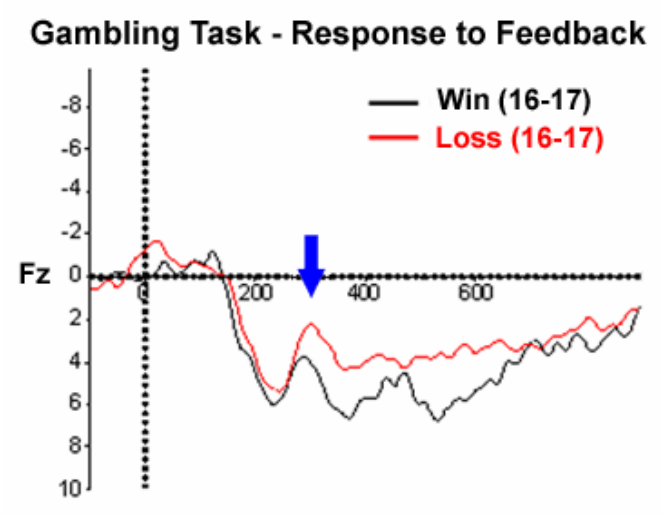


**Fig. 10** – Event-Related Potentials to Feedback in the Gambling Task. ERPs were recorded from 15 civilian controls, time-locked to the onset of feedback indicating whether they won or lost the hand. Here, ERPs from frontal midline electrode Fz are averaged across winning or losing hands of 16 and 17. The feedback negativity (FN) is indicated by the blue arrow. Negative is plotted upwards.

## Phase 5: Integrative Analysis and Presentation of Findings at Scientific Meetings and Publication in Scientific Journals

First we describe a series of analyses that examined the relationship of the participants' self-reported impulsivity to PTSD symptoms and behavioral performance. Next we note that during the funding period we wrote 6 papers (3 published, 2 submitted or under revision, and 1 draft) and presented 7 abstracts at professional meetings, as listed in the Reportable Outcomes on p. 22-23. We have enough data analyzed and presented in preliminary form (in this report) for several more manuscripts.

(A) PTSD and Impulsivity:

A lack of inhibitory control can lead to negative psychosocial outcomes and increase the risk of alcoholism, substance abuse, and suicide. Therefore, identifying veterans and active duty military personnel who have problems with impulsive behavior is of critical importance. The Barratt Impulsiveness Scale (BIS-11) is a widely used self-report instrument with separate scales for attentional or cognitive impulsiveness (inability to focus attention), motor impulsiveness (acting without thinking), and non-planning impulsiveness (lack of forethought), based on factor analytic studies (Patton et al., 1995). Elevated BIS-11 scores have been reported for clinical populations such as those with ADHD (Müller et al., 2007) and bipolar disorder (Swann et al., 2008), but no studies have examined impulsivity in the OEF/OIF population.

We correlated subscores from the BIS-11A[1] and the PCL-M to determine which symptom clusters of PTSD were related to overall impulsivity, and which aspects of impulsivity were associated with more severe PTSD. Then we used multiple regression to determine the predictors

[1] The widely-distributed BIS-11A was used inadvertently instead of the more validated BIS-11 (Stanford et. al., 2009). We used the prorating method developed by Dr. Marijn Lijffijt to score the data (http://impulsivity.org/BIS-11/bis-10r-bis-11a-issue).

of total scores on the PCL-M and BIS. We included our entire veteran population in these analyses (n=82), consisting of 48 patients and 34 controls. Results indicated that overall scores on the PCL-M and the BIS-11A were significantly correlated (r=.65, p<.0001), suggesting that more severe PTSD symptoms were associated with higher levels of impulsivity. All three symptom clusters were strongly correlated with total BIS-11A score (respective r's=.57, .62, .67 for re-experiencing, avoidance/numbing, and hyperarousal). However, when entered into a multiple regression, only hyperarousal remained as a significant predictor of impulsivity (r=.56, p=.003). The implications of these findings are that treatments that improve sleep and enhance relaxation, such as mindfulness-based training, might be the most effective in reducing impulsive behavior.

Examining the different facets of impulsivity indicated that all three were individually correlated with total PCL-M score (respective r's=.76, .45, .46 for cognitive, motor, and non-planning). However, multiple regression indicated that cognitive impulsiveness was the only significant predictor of PTSD severity (r=.70, p<.0001). This suggests that impaired attentional control might contribute to the maintenance of PTSD symptomology. These results replicate the preliminary findings reported by Dr. Karen Seal in a recent presentation given through the VA intranet (Seal, 2012).

(B) Impulsivity and Inhibitory Control:

The relationship between self-report measures of impulsivity and performance on laboratory tests of inhibitory control is unclear, and the results thus far have been contradictory (Aichert et al., 2012). We examined the correlation between BIS-11A scores and several measures of executive control function in the OEF/OIF population. For the Go/NoGo task, total BIS score was weakly correlated with false alarm errors (rho=.25, p=.02), but the cognitive impulsiveness scale was more strongly correlated (rho=.39, p=.0004). Likewise, RT variability showed a significant positive correlation with cognitive impulsiveness (rho=.31, p=.005). Neither laboratory measure was related to the construct of motor impulsiveness. In contrast, stopping performance in the Stop-Signal task was not related to any dimension of impulsivity. This replicates previous findings in a large group of control participants (Aichert et al., 2012). Although these investigators found a shared underlying construct of "pre-potent response inhibition" in a latent variable analysis, task-specific factors contribute to dissociations in behavioral performance and underlying neural substrates (see also Phase 3D and 3E above).

Decomposing the different dimensions of impulsivity at the cognitive, affective and neural levels may help identify those at greater risk for alcoholism, substance abuse, problematic gambling, and suicide. We feel it is our duty and privilege to find solutions for OEF/OIF Veterans who served in Afghanistan and Iraq, and we are hopeful that this project can contribute to that effort. Research in many of the areas described here will continue in the four year renewal of the PI's VA Merit Grant (Award Number 1I01CX000566-01A2).

KEY RESEARCH ACCOMPLISHMENTS:

- Demonstrated that the emotional Stroop task with combat-related words is a robust and sensitive measure of attentional bias to trauma-relevant material in OEF/OIF Veterans with PTSD (Ashley et al., pending revision). The enhancement of the emotional Stroop interference effect was specific for combat words, as it did not occur for general negatively-valenced words, and it correlated most strongly with the re-experiencing subscale of the PCL-M.

- The carefully matched stimulus lists used in this study will be published in an open access journal along with the manuscript. The emotional Stroop task may serve as a useful pre- and post-treatment measure in intervention studies with OEF/OIF Veterans with PTSD. We have already supplied the stimulus materials to an investigator wishing to conduct such a study.

- Published a paper reporting that OEF/OIF Veterans with PTSD were impaired in a Go/NoGo task that measures the ability to inhibit inappropriate responses (Swick et al., 2012). The co-occurrence of mTBI and PTSD did not worsen the response inhibition deficit associated with PTSD alone. The severity of self-rated PTSD and depressive symptoms correlated with the number of false alarm errors in the task.

- Observed that the PTSD patients showed significantly greater trial-to-trial variability in their reaction times in the Go/NoGo task, which suggests a reduction in the stability of executive control processes over time. The addition of mTBI(s) to PTSD did not worsen performance. A preliminary draft of the manuscript describing these results is available upon request.

- Discovered that the PTSD group performed as well as controls in the Stop-Signal task, which assesses the ability to stop a pre-planned response. This stands in contrast with the patients' impaired performance in the Go/NoGo task and suggests that these two tests measure different aspects of response inhibition. We will prepare a manuscript describing these results.

- Published a paper comparing the neural correlates of the Go/NoGo and Stop-Signal response inhibition tasks, based on a meta-analysis of the neuroimaging literature (Swick et al., 2011a). Clarifying the brain regions that implement performance of the Go/NoGo task will help identify the neural networks compromised in those with PTSD.

- Observed a strong relationship between self-reported impulsivity and the severity of PTSD symptoms in the OEF/OIF Veteran population. Specifically, the degree of hyperarousal predicted impulsivity scores. The potential clinical implications are that mindfulness-based training to improve sleep and enhance relaxation might be effective in reducing impulsive behavior.

- Published a paper on how multi-tasking affects behavioral and neural measures of visual attention in control participants (Pratt et al, 2011).

- Demonstrated that the PTSD/mTBI patients showed intact performance and ERP effects in a flanker interference task under both single-task and dual-task conditions, suggesting that some types of executive control processes are intact. We will prepare a manuscript describing these results.

- Submitted a manuscript showing that working memory performance is compromised in PTSD/mTBI patients when additional cognitive demands require multi-tasking (Honzel et al., submitted). The patients also showed a reduction in the electrophysiological substrate of working memory retrieval in the dual task condition, which correlated with the severity of re-experiencing symptoms.

- Initiated a new set of analyses of EEG activity during the encoding and delay intervals of the Sternberg memory task. Preliminary results are suggestive of spectral differences between the controls and PTSD patients during encoding. Specifically, power in the theta and alpha bands tends to be larger for controls in the dual task condition. We will prepare a manuscript describing these results.

- Demonstrated that PTSD/mTBI patients are as good as or better than controls at suppressing information that is no longer relevant, when the stimuli are neutral and unrelated to combat trauma.

- Determined that the PTSD/mTBI patients showed a slight reduction in the electrophysiological correlate of error processing, the error-related negativity (ERN), although this was not significant. The combination of co-morbid depression, PTSD, and mTBI may have had differential effects on this ERP measure.

REPORTABLE OUTCOMES:

**Publications**

Swick, D., Ashley, V., & Turken, A.U. (2011a). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *NeuroImage* 56: 1655-1665. http://dx.doi.org/10.1016/j.neuroimage.2011.02.070

Pratt, N.L., Willoughby. A., & Swick, D. (2011). Effects of working memory load on visual selective attention: Behavioral and electrophysiological evidence. *Frontiers in Human Neuroscience* 5:57. http://dx.doi.org/10.3389/fnhum.2011.00057

Swick, D., Honzel, N., Larsen, J., Ashley, V., & Justus, T. (2012). Impaired response inhibition in veterans with post-traumatic stress disorder and mild traumatic brain injury. *Journal of the International Neuropsychological Society* 18:1-10.
http://dx.doi.org/10.1017/S1355617712000458

Ashley, V., Honzel, N., Larsen, J., Justus T., & Swick D (pending revision). Attentional bias for trauma-related words: Exaggerated emotional Stroop effect in Afghanistan and Iraq war veterans with PTSD. *BMC: Psychiatry*.

Honzel, H., Justus, T. & Swick, D. (submitted). Post-traumatic stress disorder is associated with reduced executive control in a working memory task.

Swick, D., Honzel, N., Larsen, J., & Ashley, V. & Justus, T. (draft). Increased response variability as a marker of executive dysfunction in veterans with post-traumatic stress disorder and mild traumatic brain injury.

**Abstracts**

Swick, D., Ashley, V., & Turken, A.U. (2009a). Response inhibition and the inferior frontal gyrus: Are there task differences in lateralization? Poster presented at the Cognitive

Neuroscience Society meeting, March 21-24, 2009. (p. 104)

Swick, D., Ashley, V., & Turken, A.U. (2009b). Lateralization of response inhibition in the inferior frontal gyrus: It's not always right. *Human Brain Mapping*. http://dx.doi.org/10.1016/S1053-8119(09)71942-1

Swick, D., Ashley, V., Pratt, N., Larsen, J., & Justus T. (2009c). Attentional Bias and Response Inhibition in Veterans with Post-Traumatic Stress Disorder and Traumatic Brain Injury. Abstract presented at the Military Health Research Forum, Aug 31 – Sept 3, 2009.

Pratt, N., Willoughby, A., & Swick, D. (2010). When the going gets tough, attention starts going. Poster presented at the Cognitive Neuroscience Society meeting, April 17-20, 2010.

Ashley V, Swick D, Pratt N, Larsen J, Justus T. (2011). Attentional bias for trauma-related words: Exaggerated emotional Stroop effect in Iraq and Afghanistan war veterans with PTSD. Poster presented at the Cognitive Neuroscience Society Meeting, April 2011.

Swick D, Ashley V, Turken AU. (2011b). Performance on Go/NoGo and Stop-Signal response inhibition tasks is not correlated. Poster presented at the Cognitive Neuroscience Society Meeting, April 2011.

Ashley V, Larsen J, Pratt N, Swick D. (2012). Impaired identification of facial expressions of fear in Iraq war veterans with PTSD and mTBI. Poster presented at the Cognitive Neuroscience Society Meeting, March 31 – April 3, 2012.

**Presentations**

October 14, 2008: Neurobehavioral Brown Bag Lunch at VANCHCS in Martinez.

October 27, 2008: Neurobiology, Physiology, and Behavior faculty seminar series at the University of California, Davis.

September 3, 2009: Attentional Bias and Response Inhibition in Veterans with Post-Traumatic Stress Disorder and Traumatic Brain Injury. Military Health Research Forum, Kansas City.

August 18, 2009: Neurobehavioral Brown Bag Lunch at VANCHCS in Martinez.

December 17, 2009: Neurology Grand Rounds at the University of California, Davis Medical Center in Sacramento.

April 28, 2010: Featured speaker at VA Research Day in Martinez: "Brain and Behavioral Changes in Veterans with PTSD and TBI: Towards Better Diagnosis and Treatment." Members of my lab manned a booth explaining our research to other employees, veterans, and members of the public. These Research Day activities led to interviews and press coverage in *Contra Costa Times*: "VA medical center in Martinez a locus for research into traumatic brain injury." Archive: http://vmwusa.org/index.php/vetservices/vsarticles/46-veteranservices/718-tbi

November 4, 2010: VA/DoD Annual Conference at Travis Air Force Base/David Grant Medical

Center. The theme was "Behavioral Health Across the Continuum and the Generations." My presentation was on "Brain and Behavioral Changes in Veterans with PTSD and TBI: Towards Better Diagnosis and Treatment."

November 2010: Data from this project were presented by Dr. Anthony Chen at a DoD/TATRC meeting in San Francisco.

Feb 15, 2011: Data presented at TBI Journal Club, VANCHCS Martinez

September 14, 2011: TBI Cognitive Rehabilitation In-Process Review, Herndon, VA

Feb 7, 2012: Data presented at TBI Journal Club, VANCHCS Martinez

Sept 20, 2012: Cognitive and Neurophysiological Effects of Mild TBI and PTSD in Returning Veterans, UC Davis Neurology Grand Rounds

**Grant Applications**

*The Behavioral and Neurophysiological Effects of Concussions in Athletes*. Submitted to the Gustavus and Louise Pfeiffer Research Foundation on 8/27/09, not funded. *Principal Investigator*: Diane Swick, Ph.D. *Co-PI*: Nikki Pratt, Ph.D.

*When does a concussion produce long-term consequences? Using an objective biomarker to detect post-concussive syndrome in athletes.* Submitted to NFL Medical Research Grants on 6/10/10, not funded. *Principal Investigator*: Nikki Pratt, Ph.D. *Co-PI*: Diane Swick, Ph.D.

*Neural correlates of gambling behavior following traumatic brain injury: Implications for pathological gambling*. Submitted to Institute for Research on Gambling Disorders on 7/1/10, not funded. *Principal Investigator*: Nikki Pratt, Ph.D. *Mentor*: Diane Swick, Ph.D.

*The impact of cognitive deficits in TBI and PTSD on language comprehension*. VA Career Development Award submitted to RR&D on 6/6/11, not funded. *Principal Investigator*: Timothy Justus, Ph.D. *Mentor*: Diane Swick, Ph.D.

*Electrophysiological markers of concussion symptoms in NFL players.* Submitted as Pre-Proposal for NFL Medical Research Grants on 8/17/11, not internally selected by UC Davis. *Principal Investigator*: Diane Swick, Ph.D. *Co-PI*: Nikki Pratt, Ph.D.

*The Structure and Function of the Anterior Cingulate Cortex in PTSD*. VA Career Development Award submitted to RR&D on 12/6/11, not funded. *Principal Investigator*: Nikki Honzel, Ph.D. *Mentor*: Diane Swick, Ph.D.

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CONCLUSION:

Executive control over cognition and emotion is critical for avoiding undesirable behavioral response patterns at home, school and work. These cognitive processes are also essential to facilitate recovery from traumatic events and brain injuries, so veterans can return to their usual social and occupational activities. Separating the negative effects of PTSD and mTBI on executive control functions has been difficult, due the paucity of veterans who have probable mTBI due to blast exposure in the absence of PTSD and other psychiatric symptoms. The majority of veterans recruited at VANCHCS have mTBI+PTSD (71%), with 23% diagnosed with PTSD only, and a mere 6% with mTBI only. Does mTBI increase vulnerability to PTSD due to brain injury, or because both conditions involve exposure to traumatic events in the military theater? Although it is impossible to determine causality from our results, we and others have observed no differences in PCL-M scores in PTSD patients with vs. those without co-morbid mTBI. Furthermore, the severity of mTBI (number, loss of consciousness) did not affect PCL-M scores (Swick et al., 2012).

Three areas emerged where the PTSD/mTBI participants showed strengths in executive control functions: overriding conflicting response cues in a flanker task (see Phase 4B), overcoming proactive interference in working memory, i.e., suppressing material that is no longer relevant (Phase 4E), and stopping a motor response that was already planned (Phase 3D).

These strengths are closely related to other executive functions that were weaker in the PTSD/mTBI participants. They showed pronounced deficits in motor response inhibition (Phase 3B), consistency in responding (Phase 3C), and control over emotional reactions to trauma reminders (Phase 3A). Although they were not uniformly impaired in multi-tasking (Phase 4B), the patients showed behavioral and electrophysiological deficits in working memory retrieval that became apparent when they performed a secondary task during the delay interval (Phase 4C).

Impairments in executive control have great clinical importance because even subtle deficits can influence coping style and cognitive reappraisal strategies. We examined the relationship between performance and the three symptom clusters of PTSD. The avoidance/numbing cluster shares symptoms with major depression, and hyperarousal shows some overlap with generalized anxiety disorder, while re-experiencing is most unique to PTSD. All of the above impairments showed the strongest correlations with the severity of re-experiencing symptoms: intrusive thoughts, flashbacks, and nightmares about the traumatic events. Limitations in executive processing may contribute to the inability of individuals with PTSD to disengage from traumatic memories.

Ultimately, the types of dissociations observed here are informative for theoretical models of executive control function, but more importantly for demonstrating that PTSD/mTBI can spare some important cognitive abilities. These strengths could be exploited in future developments of psychotherapy and cognitive rehabilitation techniques.

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# APPENDICES

**Manuscripts:** **Page**



**Abstracts:**

# Attentional bias for trauma-related words:

# Exaggerated emotional Stroop effect in Afghanistan and Iraq war veterans with PTSD

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**Abstract**

Post-traumatic stress disorder (PTSD) involves debilitating symptoms that can disrupt cognitive functioning. The emotional Stroop has been commonly used to examine the impact of PTSD on attentional control, but no published study has yet used it with Afghanistan and Iraq war veterans, and only one previous study has compared groups on habituation to trauma-related words. We administered the emotional Stroop, the Beck Depression Inventory (BDI), and the PTSD Checklist (PCL) to 30 veterans with PTSD, 30 military controls, and 30 civilian controls. Stroop word types included Combat, Matched-neutral, Neutral, Positive and Negative. Results indicated that veterans with PTSD were disproportionately slower than controls on Combat words, were slower and less accurate overall, did not show interference on Negative or Positive words relative to Neutral, and showed a trend for delayed but successful habituation to Combat words. Higher PCL and BDI scores also correlated with larger interference effects. The emotional Stroop task may serve as a useful pre- and post task with intervention studies of PTSD patients.

Keywords: Posttraumatic stress disorder, PTSD, Stroop, Habituation, Trauma, Interference

# Attentional bias for trauma-related words:
# Exaggerated emotional Stroop effect in Afghanistan and Iraq war veterans with PTSD

Numerous studies have examined the cognitive and emotional impact on the estimated 10 to 17% of US service members who have returned from the wars in Iraq and Afghanistan with post-traumatic stress disorder (PTSD) [1-3]. However, no studies that we are aware of have used the emotional Stroop to assess this population, a task commonly used to examine attention biases in anxiety and depressive disorders, including PTSD [4-6], and particularly in war veterans with PTSD [7-13]

The combat theaters of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) in Afghanistan and Iraq involved multiple and extended deployments with shorter rest periods, higher wound survivability rates, and large numbers of traumatic brain injuries (TBI) than previous US wars [2]. PTSD is a disorder involving long-term alteration of physiological and emotional functioning following exposure to horrific events, and typically involves intrusive cognitive and emotional phenomena such as nightmares, flashbacks, memory deficits and biases in attentional allocation [14]. Mechanisms that may underlie the attentional biases in PTSD include regulating, inhibiting or extinguishing a fear response following trauma exposure [15-17].

The emotional Stroop task, a variant of the classic Stroop task, indexes emotional interference by comparing reaction time (RT) differences to name the font color of an emotional word compared to a neutral word, with instructions to ignore the meaning of the word. Healthy individuals are typically slower to name the colors of negative-valenced words [18], and this effect is often robust in individuals with PTSD when color-naming trauma-related words [4-6] (however, see [19]). The emotional Stroop task has also been shown to be sensitive to malingering -- Buckley, Galovski, Blanchard & Hickling

(2003) [20] covertly enrolled professional actors trained to feign PTSD into a treatment outcome study, and found that the actors were unable to replicate the interference effects displayed by the trauma survivors with PTSD.

The mechanisms of interference in the emotional Stroop task have been debated. While earlier studies concluded that emotional words capture attention [10-11,21], later studies have found that emotional words are more difficult to disengage from [22-23]. Other studies suggest roles for both attentional capture and difficulty in disengagement [24]. Being unable to disengage from irrelevant stimuli can not only impact daily life, i.e., the need to focus on the changing color of a traffic light when approaching a busy intersection. In addition, if attention is diverted sooner and longer by trauma-related reminders, this may contribute to maintaining attentional biases.

The intractable nature of the response to trauma reminders in PTSD is often cited as a hallmark of the disorder, involving a unique difficulty for PTSD sufferers to habituate, or adapt to, such reminders. For example, some veterans with PTSD who participated in our study described experiencing overwhelming feelings of anger and fear upon getting caught in traffic jams, because it reminded them of their vulnerability to roadside explosive attacks in Iraq. Despite knowing that roadside bombs would not occur in the US, the debilitating overwhelming emotional response was inevitable. Such an inability to habituate to day-to-day trauma reminders is believed to contribute to the persistence of PTSD. Studies of habituation in PTSD typically find physiological differences in response to trauma-related stimuli (but less so for general negative stimuli) and reliably indicate an altered profile of persistent hyper-arousal, exaggerated startle responses [16,25], larger eye-blink, eye pupil, heart rate and slower skin conductance habituation [26].

While most studies of habituation to trauma-related stimuli in PTSD have measured physiological responses, at least one has used the emotional Stroop [27]. Habituation using the

emotional Stroop is defined as diminished emotional interference effects (less RT slowing) combined with increased RT slowing for neutral words, or fatigue effects, over time [11,28]. The emotional Stroop has been used to assess habituation to relevant emotional words with healthy adults [29], individuals with panic disorder [11], individuals with elevated health anxiety [28] and veterans with PTSD [27]. McNally, Amir & Lipke (1996) [27] compared RTs by Vietnam combat veterans with and without PTSD over 4 mixed blocks of words (96 words each), in response to 4 word types: trauma, positive, neutral and color words. In a block by block comparison, they found that PTSD patients showed trauma-specific interference effects on the first block, and then habituated to the content of the trauma words over time, becoming indistinguishable from controls by the end [27].

PTSD patients often show significant interference to only trauma-related stimuli, rather than general negative or threat-related stimuli [10-11], however, studies do not agree on this finding [5,19]. For example, Litz et al. (1996) [9] found Stroop interference effects for veterans color-naming high-threat words unrelated to their trauma, suggesting that PTSD patients may display interference effects from all high-threat words, rather than just trauma-related words. Findings that PTSD patients show a specific bias for trauma-related words, and not generally negative or threatening words, supports the idea that the emotional Stroop may index PTSD, rather than exposure to trauma (with or without PTSD). In order to examine the apparent specificity in PTSD for threat-related words in the current study, rather than using only threat-related and matched neutral words, we used five different word types: Combat, Matched-neutral, Negative, Positive and Neutral. Combat and Matched-neutral were each compared, and then separately, Negative, Positive and Neutral were each compared. This separation kept variables such as word frequency, valence, arousal, and other properties as consistent as possible across comparisons. Furthermore, many emotional Stroop studies of PTSD have included small numbers of words and have repeated them. However, when words are repeated, a potential

confound is introduced between whether any observed habituation is due to perceiving the same word more than once, or to adapting to the semantic content of the word, or both. Consequently, we used all unique words in the current study.

Having a military control group (MC) that experienced the same trauma environment as PTs was important to distinguish between trauma exposed individuals with and without PTSD (13 out of 30 MCs were deployed to Iraq or Afghanistan during the OEF/OIF wars). Additionally, to reveal any possible Stroop effects due to military work conditions and lifestyles, we also included a healthy civilian control group (CC).

The primary goal of our study was to expand on the dominant findings of the majority of emotional Stroop studies with PTSD patients, in which, compared to controls, PTSD patients exhibit significant interference (RT slowing) and increased errors on trauma-related words. First, given the specificity of the deficit in PTSD to trauma-related stimuli, we predicted that veterans with PTSD would show less interference from Negative words relative to Neutral, then from Combat words relative to Matched-neutral. Next, in keeping with one previous study examining habituation to trauma words with an emotional Stroop [27], we also expected veterans with PTSD to show diminished habituation to Combat words relative to controls. Finally, we predicted that Stroop interference would correlate positively with scores on the PTSD checklist (PCL) and the Beck Depression Inventory (BDI) for all subjects.

## METHODS

### Participants

(Table 1 about here)

Thirty OEF/OIF war veterans with PTSD (29 males) (PTs), thirty age-matched military controls (28

males) (MCs), and thirty age-matched civilian controls (30 males) (CCs), participated in the study. Demographic information is shown in Table 1. PTSD diagnosis was based on a clinical interview using DSM-IV criteria. Mild TBI was diagnosed based on a clinical interview and patient self-report of the following criteria from the VA/DoD Clinical Practice Guidelines – loss of consciousness 30 min or less or altered mental status (e.g., feeling dazed, disoriented, or confused), with post-traumatic amnesia less than 24 hrs [30]. Twenty-two of the 30 PTSD patients reported or were diagnosed with a mild traumatic brain injury (TBI), typically due to IED blast exposure. Diagnoses of mTBI and PTSD were corroborated with available VA medical records to the fullest extent possible.

Participants were recruited from clinics at the Veterans Affairs of Northern California Health Care System, fliers placed in local military offices, and internet postings. Subjects signed informed consent forms approved by the Institutional Review Board of the Veterans Affairs Medical Center and were paid $20/hr plus travel after completion of the session. Control groups were matched for age and gender but not education ($p<.0003$). Previous emotional Stroop studies of veterans with PTSD have also noted difficulty in matching groups of veterans on years of education (e.g., [11,13]. Exclusion criteria included any neurological or additional psychiatric disorders (i.e., schizophrenia, bipolar, epilepsy), or having PTSD not due to OEF/OIF events (i.e., due to the Vietnam war, car accident, etc.). Six participants who were initially enrolled were subsequently removed from the study (4 patients, 2 controls), when it was found they met exclusionary criteria (childhood TBI; nonmilitary PTSD; moderate TBI; other psychiatric disorder; not OEF/OIF). Two other participants did not complete the emotional Stroop task and were also subsequently removed from the study (2 patients). All subjects reported English as their first language.

**Materials**

Following the emotional Stroop task, subjects were asked to complete the 17-item PTSD Checklist,

Military or Civilian Version (PCL-M or PCL-C) to assess their level of PTSD symptoms during the past month. The PCL is a widely used 17-item self-report measure of the DSM-IV symptoms of PTSD [31]. Patients and military controls received the PCL-M (military), which asks about symptoms they have been bothered by in the past month due to "stressful military experiences". The PCL-C (civilian) was given to civilian controls and asks about symptoms in response to "stressful experiences". All subjects were also given the Beck Depression Inventory (BDI; [32]), to assess levels of depression in the past few days. The BDI is a commonly used 21-item self-report screen for major depressive disorder (MDD) that has been validated with well-established psychometric properties [33].

Stimuli were colored words (red, blue, green, or yellow) shown one at a time in the center of a computer screen in 48 pt Times font, using all capital letters, on a black background at a distance of approximately 30 cm from the viewer. Colors did not repeat on consecutive words and were equally used throughout all trials. The task included 5 blocks of words, with each block containing a single word category. The five categories of words were: 1) “Combat”: trauma-related words based in events of the OEF/OIF wars in Iraq and Afghanistan (i.e., *detainee, warlord, Falluja*); 2) “Matched-neutral”: words matched to combat words in number of letters and frequency (i.e., *detective, faculty, Jakarta*); 3) “Positive” (i.e., *proud, comedy, diamond*); “Negative” (i.e., *fraud, stupid, tragedy*) and “Neutral” (*sleep, poster, mixture*).

Combat and Matched-neutral words: We created the Combat word list from a search of mainstream media news stories, soldier blog entries, and other public sources describing unique and traumatic aspects of the OEF/OIF war experience. Typical OEF/OIF combat stressors included exposure to improvised explosive device (IED) blasts and suicide bombers, seeing human remains, engaging in killing another person, experiencing violent deaths and injuries of fellow soldiers and

friends, and being unable to stop violent situations [3]. Four types of Combat words were used: 1) Words associated with the OEF/OIF combat events (i.e., *insurgent*), 2) Place names (i.e., *Kirkuk*), 3) Military abbreviations (i.e., *IED*), and 4) General war trauma words (i.e., *gunmen*). Matched-neutral words were created by finding words neutral in valence to match Combat words on number of letters, syllables, word type and frequency (see Appendix A).

Neutral, Negative and Positive words: Neutral, Negative and Positive words were matched on number of letters, number of syllables and frequency. Only high arousal Negative and Positive words were used and arousal and valence ratings for Neutral, Negative and Positive words were based on the Affective Norms for English Words [34]. ANOVAs were conducted to examine any word type differences. Mean valence ratings were as follows: Positive: 7.6 (SD=0.5, range=7.0–8.7), Negative: 2.6 (SD=0.6, range=1.3-3.9) and Neutral: 5.3 (SD=1.1, range=1.9-7.9). Arousal levels for both Positive (mean=5.8, SD=0.6) and Negative words (mean=5.8, SD=0.9) were higher than Neutral (mean=3.6, SD=0.4) ($p<.0001$). No significant differences between word categories were found using the Hyperspace Analogue to Language (HAL) frequency norms ($p=0.69$) from the online database of the English Lexicon Project (ELP) [35].

**Procedure**

All participants were instructed to name the color of a word shown on the computer screen by speaking into a voice-activated microphone as quickly and as accurately as possible. Participants started with 15 neutral word practice trials. Words were presented for 500 ms using Presentation software (Neurobehavioral Systems Inc., CA, USA), with a total trial time of 2000 ms and an inter-stimulus interval of 1500 ms. Each of the 5 blocks contained 84 words for a total of 420 unique words. Each block took approximately 3 minutes to complete and the study lasted between 15 and 20 minutes.

Within blocks, words were presented in fixed pseudo-randomized order.

Because emotional stimuli can contaminate later non-emotional stimuli with carry-over slowing effects, the order of presentation of trials and blocks in an emotional Stroop study should attempt to counterbalance such effects [28,36]. We used a Latin Square design employed by McKenna and Sharma [29,37] to counterbalance order effects of different word types in a blocked design format across all participants. Blocks were counterbalanced using a balanced 5 x 5 Latin Square design [38] [39] in which subjects received one of 10 possible block orders (5 block orders mirrored the other 5). Each of the 10 different Latin Square orders was repeated 3 times within each group (n=30). The PCL and BDI questionnaires were administered on paper after the Stroop task.

## RESULTS

Only correct responses were included in results analyses (average percentage of error RTs removed: PTSD PTs=3.53%; Military Controls=1.56%; Civilian Controls=1.61%). Behavioral exclusion criteria included participants with more than 25% error rates [40] and no participants met that level. Trial reaction time data were trimmed to decrease variance such that RTs longer than 2 SDs above the subject's block mean were removed (average removed: PTs=5.3%; MCs=5.4%; CCs=5.3%) [41], and RTs beyond 3000 ms or faster than 200 ms (i.e., coughs) [42], were removed (average removed: PTs=4.3%; MCs=3.6%; CCs=3.0%).

Reaction time and accuracy were each examined with a 3 x 5 Mixed Repeated Measures ANOVA, with Group (PTs, MCs, CCs) as the between-subjects factor and Word Valence (Combat, Matched-neutral, Neutral, Negative, Positive) as the within-subjects factor. When contrasts were not planned, a correction for multiple comparisons of $p<.005$ was used.

**Reaction times**

Color-naming

Reaction time results indicated a significant main effect of Group, $F(2,87)=7.75$, $p=.0008$, with overall RTs for PTs slower than either Control group (Means: PTs=726 ms, MCs=604 ms, CCs=599 ms). A significant main effect was also shown for Valence, $F(4,8)=26.16$, $p<.0001$, with all groups slower on Combat words relative to Matched-neutral words ($p<.02$), confirming the emotional Stroop effect (see Fig 1). An interaction effect for Valence x Group, $F(8,348)=3.87$, $p=.0002$, indicated that group RTs differed depending on word type, with PTs showing greater slowing for Combat versus Matched-neutral than controls.

(Figure 1 about here)

*Combat and Matched-neutral:* Within group planned paired t-test comparisons of Combat and Matched-neutral blocks showed that each group was slower on Combat words: PTs: $t(1,29)=6.47$, $p<.0001$; MCs $t(1,29)=2.81$, $p=.009$; and CCs $t(1,29)=2.63$, $p=.01$. A between-groups ANOVA analysis of RTs to Combat and Matched-neutral blocks showed a robust interaction of Valence x Group, $F(2,87)=8.53$, $p=.0004$, indicating that although all groups were slower on Combat words, PTs had greater slowing than either control group.

*Neutral, Positive and Negative:* Between group ANOVAs examining mean RTs on Negative versus Neutral and Positive versus Neutral blocks showed main effects of Group [Negative: $F(2,87)=7.18$, $p=.001$; Positive: $F(2,87)=6.76$, $p=.002$], with PTs significantly slower overall, but no significant group interactions (Negative: $p=.11$; Positive: $p=.08$). Within group planned paired t-test comparisons indicated that MCs were slower on Negative versus Neutral, $t(1,29)=3.67$, $p=.001$, and had a non-significant trend for being slower on Positive versus Neutral, $t(1,29)=1.81$, $p=.08$. CCs showed no significant differences on Negative versus Neutral, ($p=.61$), or Positive versus Neutral ($p=.405$). PTs were significantly slower on Negative versus Positive, $t(1,29)=1.79$, $p=.009$, and MCs

displayed a trend for the same finding, $t(1,29)=1.79$, $p=.083$ (see Table 2).

(Table 2 about here)

Thus, PTs did show a large interference effect on Combat words (112 ms; $p<.0001$) but not on Negative relative to Neutral (19 ms; $p=.18$). In contrast, MCs showed interference effects of a similar size on both Combat (41 ms; $p=.009$) and Negative (41 ms; $p=.001$) and CCs showed an interference effect by Combat words similar to MCs (33 ms; $p=.01$) but no other significant effects.

To test whether the lower education in the PT group affected the findings of the study, we examined a subset of both control groups with lower education (n=32) to match with the PT group [mean education in years: PTs: 13.12; MCs: 13.44; CCs: 13.3 ($p>.41$)] and found that overall group RTs were still significantly different, $F(2,59)=4.83$, $p=.01$, and that the Group x Valence interaction still existed, $F(8,236)=2.26$, $p=.02$. The results were the same for the error analysis: while overall group accuracy was still significantly different, $F(2,59)=6.12$, $p=.004$, the Group x Valence interaction did not reach significance, $F(8,236)=.886$, $p=.53$. Only 7 MCs reported active combat, whereas all of the veterans with PTSD reported active combat. A between-groups ANOVA (MCs Deployed versus MCs Not Deployed) analysis of RTs did not find any overall group differences ($p=.29$) or Group x Valence interaction ($p=.11$). However, because the Latin Square order is not balanced in this type of analysis, the validity of such comparisons is difficult to determine.

Habituation

We analyzed habituation effects across the length of the Combat and Matched-neutral blocks (84 trials each) by comparing average RTs during each quarter of the blocks: “First quarter” (trials 1-21), “Second quarter” (trials 22-42), “Third quarter” (trials 43-63) and “Fourth quarter” (trials 64-84). The choice of quarters was based on the number of trials in the habituation analysis by Witthöft, et al. (2008) [28], which compared groups during the first and second halves of blocks (trials 1-20 and 21-

40), and the emotional Stroop studies by McNally, Riemann & Kim (1990) [43] and McNally, Amir & Lipke (1996) [27], which analyzed 4 different word types, each occurring on 20 and 24 trials per mixed block (with each block being 100 and 96 trials in length), respectively.

We analyzed RTs in a repeated measures 3 (Group) x 4 (Quarter) x 2 (Valence) ANOVA. Results showed an interaction effect of Valence x Group ($p$=.0008), no interaction of Quarter x Group (p=.54), and a trend for the 3-way interaction of Quarter x Valence x Group ($p$=.09) (See Fig 2). Planned t-test comparisons confirmed that PTs were slower on Combat than Matched-neutral words on all quarters, Q1: $t(1,29)=5.1$, $p<.0001$; Q2: $t(1,29)=5.0$, $p<.0001$; Q3: $t(1,29)=5.1$, $p<.0001$; Q4: $t(1,29)=2.9$, $p=.007$, while both control groups were slower only on quarter 1 (MCs: $t(1,29)=2.8$, $p=.01$; CCs: $t(1,29)=2.7$, $p=.01$), with intermittent slowing on other quarters (MCs: Q4, $p=.02$; CCs: Q3, $p=.005$).

(Figure 2 about here)

In an analysis similar to McNally, Amir & Lipke (1996) [27], who found that trauma-related interference for veterans with PTSD was apparent only on the first of four blocks, we analyzed each quarter using a 2 (Group) x 2 (Valence) repeated measures ANOVA. Results indicated a significant Valence x Group interaction on quarters 1 – 3 (Q1: $F(2,87)=6.48$, $p=.002$; Q2: $F(2,87)=6.7$, $p=.002$; Q3: $F(2,87)=7.24$, $p=.001$), but not on quarter 4 (Q4: $F(2,87)=1.81$, $p=.17$). PTs showed a strong interference effect (over 120 ms) from Combat words during the first 3 quarters of the block, which decreased to 64 ms in the last quarter (See Fig 2), while control groups never showed more than 41 ms of interference slowing (See Table 3).

(Table 3 about here)

These results suggest that although veterans with PTSD displayed a tendency for exaggerated interference effects from trauma-related stimuli across the full length of the block, by the last quarter,

the groups were no longer different. Thus, PTs tended to differ from controls for up to 63 trials, but appeared to habituate in the last quarter of the block.

**Accuracy**

An ANOVA conducted for accuracy scores showed a significant main effect of Group $F(2,87)=9.99$, $p=.0001$, indicating that PTs were less accurate than Control groups overall (average percent accuracy: PTs: 96.6; MCs: 98.4; CCs: 98.5). A main effect of Valence was also shown, $F(4,8)=4.87$, $p=.0008$, in which PTs were significantly less accurate than controls on four of the word types ($p<.04$) with a trend for Neutral as well ($p>.07$). A trend for a Group x Valence interaction was indicated ($p=.11$). Planned t-test comparisons of accuracy on Combat words showed that PTs were less accurate on Combat words relative to Control Groups, $t(1,58)=-3.1$, $p<.003$.

A speed-accuracy trade-off analysis using Spearman correlations indicated that CCs exchanged accuracy for speed on the Combat and Matched-neutral blocks: $r(1,28)=.425$, $p=.02$, while the trade-offs for PTs and MCs did not reach significance ($p$'s$>.119$). No other word types showed any significant speed-accuracy trade-off outcomes.

*Combat and Neutral Combat:* Planned paired t-test comparisons of Combat and Matched-neutral words within each group indicated a trend for PTs to be less accurate on Combat words, $t(1,29)=1.97$, $p=.06$, and no differences for Control groups, (MCs:$p=.54$; CCs: $p=.77$).

*Neutral, Positive and Negative:* Planned paired t-test comparisons within each group for Neutral, Positive and Negative words revealed no accuracy differences ($p>.14$).

**Self-Report questionnaires**

PTSD patients reported higher PCL scores (58.1) than the military (27.1) or civilian (26.0) control groups, $F(2,87)=51.2$, $p<.0001$ (PTs vs MCs: $t(1,58)=10.6$, $p<.0001$; PTs vs CCs: $t(1,58)=-11.3$, $p<.0001$) and higher BDI scores (20.4) than the military (6.3) or civilian (3.0) control groups, $F(2,87)=$

85.1, $p<.0001$ (PTs vs MCs: $t(1,58)=6.78$, $p<.0001$; PTs vs CCs: $t(1,58)=-9.4$, $p<.0001$). Bonferroni corrected comparisons between control groups indicated a non-significant trend for differences in depression on the BDI and no significant differences on the PCL (BDI, $p=.07$; PCL, $p=.70$).

**Correlations between experimental and self-report measures**

Spearman correlations conducted between the PCL and BDI self-report measures and behavioral performance indicated interference from Combat words (larger RT difference for Combat minus Matched-neutral blocks) correlated positively with increased depression scores on the BDI (*rho*=.36; $p=.0007$), and PTSD symptoms on the PCL (*rho*=.33; $p=.002$). Within the PCL, the PTSD symptom clusters of re-experiencing (*rho*=.38; $p=.0005$), hyper-arousal (*rho*=.33; $p=.002$), and avoidance/numbing (*rho*=.25; $p=.02$) also showed significant positive correlations.

## DISCUSSION

We found that OEF/OIF veterans with PTSD had significantly more interference on trauma-related words relative to controls and displayed slower RTs and lower overall accuracy, replicating the findings of several previous studies using the emotional Stroop task with veterans with PTSD [7-13] Veterans with PTSD did not show interference on Negative or Positive words relative to Neutral, suggesting that their emotional Stroop response was specific to Combat words. They also tended to display habituation to these same Combat words, despite each word being novel and relatively specific to the OEF/OIF trauma environment. Additionally, across groups, responses on the PCL and BDI questionnaires were positively correlated with percent interference slowing on Combat words, suggesting that increased severity of PTSD and depression symptoms were related to increased difficulty in inhibiting emotional interference on the task.

Our study differed from most previous emotional Stroop studies of PTSD in that all groups --

rather than only veterans with PTSD -- showed significant interference from Combat words. This outcome may be due to the use of particularly salient and intense trauma-related words (i.e., *decapitate, abduct, severed, torture)* and that none of the words repeated. Many studies of PTSD using the emotional Stroop use fewer and less unique words (i.e., *medevac, firefight)* and / or use words which are repeated [10,13,27-28]. This design was used to assist in finding habituation effects, which could be diminished or confounded if words were repeated. It also delineated larger interference effects, as indicated by the fact that all groups showed interference effects to Combat words, and that despite this, PTs still had a significantly larger interference effect relative to controls.

Our study also examined habituation effects (RT decrease to Combat words) to assess the impact of trauma-related stimuli on veterans with PTSD over time. Hyperarousal and hypervigiliance are characteristics of PTSD which may contribute to deficits in habituation, resulting in difficulty adapting to repeated exposure to trauma-related stimuli. We found that veterans with PTSD exhibited consistently strong interference to Combat words (over 120 ms) for up to 63 trials. The only other study to use the emotional Stroop to examine habituation to trauma-related stimuli for veterans with and without PTSD over time [27], found group differences, but only in the first of 4 blocks, and only as a linear pattern of RT decreases over time. However, that study included just 12 different trauma-related words repeated 8 times using a mixed, rather than pure, block design. It is likely that methodological differences, as well as the novel, intense and trauma-specific nature of our word stimuli, led to the persistent substantial interference effects seen in the current study. Importantly, however, despite the initial impact of the words, veterans with PTSD did tend to habituate and reach a color-naming response rate statistically indistinguishable from controls by the last quarter of the Combat block.

Veterans with PTSD also showed significantly slower response times overall, relative to

controls. This finding is supported by other studies using the emotional Stroop to assess PTSD, which have found that generally, PTSD participants respond slower relative to healthy controls [12-13,42]. A recent study using a classic Stroop with OEF/OIF veterans with co-morbid PTSD and TBI [45] also found overall slowing in PTSD patients. And interestingly, the results on a GoNoGo task administered to all subjects in this study indicated a striking lack of mean RT differences between PTs and controls, although the PTSD patients had significantly more variability and errors [46]. Whether the overall slowing in our study could be due to the involvement of trauma-related emotional content, or some other factor, cannot be determined and remains to be examined in future research.

The question of whether emotional Stroop interference from trauma-related words reflects specific characteristics of PTSD, or only the consequences of exposure to traumatic events, has been debated in the literature. Kimble et al. (2009) [19] has argued that RT differences seen in an emotional Stroop may be due to a self-relevant event, the trauma, and not to PTSD. And a recent study on visual attention to threatening stimuli, by Kimble, Fleming, Bandy, Kim & Zambetti (2010) [47], using eye-tracking, found that Iraq veterans with PTSD were biased towards all negatively valenced stimuli, rather than just Iraq-specific stimuli. Similarly, a meta-analysis by Cisler et al. (2011) [5] suggests that the emotional Stroop task indexes exposure to trauma, rather than PTSD itself. However, several other studies have found results supporting the idea that the emotional Stroop can index PTSD specifically [23,43,48-49].

In our study, the impact of trauma-related material on PTs appeared to eclipse the effects of Negative words, with Combat words generating much larger interference effecta then Negative words. Veterans with PTSD sometimes reported feeling as though they were “awoken” by exposure to the Combat words, relative to the other blocks, and were perplexed by the experience in which they “could not take their eyes off the words”. Importantly, PTs showed no difference on Negative relative to

Neutral words, an effect opposite to standard emotional Stroop results using a blocked design (McKenna & Sharma, 2004; Phaf & Khan, 2007). In contrast, MCs displayed the same slowing on Negative relative to Neutral as they did to Combat-related relative to Matched-neutral words (41 ms each). That the elevated emotional Stroop effect in PTs was specific to Combat words and did not generalize to other negative words, is supported by other studies that have found that the emotional Stroop task can index PTSD specifically [23,43,48-49]. Other factors related to PTSD may also be involved in these results, such as numbing. For example a recent study of perceptual processing advantages for trauma-related information (but not for general threat pictures) in patients with PTSD and Acute Stress Disorder suggested that reduced awareness of stimuli considered safe and normal may play a role in the development and persistence of PTSD [50].

It should be noted that any study investigating groups of war veterans may be limited by the availability of a completely comparable control group – that is, healthy veterans deployed to the war zone, engaged in active combat and exposed to trauma, but without PTSD or TBI and available and motivated to participate in research. Within our group of 30 MCs, 13 were deployed to Iraq or Afghanistan and exposed to the OEF/OIF combat environment, without PTSD or TBI. In the case of the OEF/OIF wars, studies suggest that the factor of deployment alone (without combat or injury), compared with non-deployment, has been associated with neuropsychological compromise on basic cognitive tasks [51]. However, in our study there were no differences between MCs who were deployed (and potentially exposed to traumatic events) and those who were not.

The importance of diagnosing and treating PTSD cannot be understated. As a disorder involving high levels of stress, PTSD is associated with alterations in the hypo-thalamic pituitary-adrenal (HPA) axis and cortisol levels [52], increased coronary atherosclerosis and myocardial infarction [53], and a nearly 2-fold-higher risk of developing dementia [54]. Sher and Yehuda (2011)

[55] also cite a "suicide epidemic" among OEF/OIF veterans due to the extreme stress of deployment. Treatments for veterans with PTSD in particular must address not only the characteristic hyperarousal, hypervigilance and numbing symptoms, but also the various physiological alterations from deployment and prolonged stress, such as chronic sleep restriction and reversed circadian cycles [56]. The results of the current study indicate that, despite these many challenges, veterans with PTSD do appear to habituate to trauma-related stimuli over time, a finding in line with broad support for exposure therapy treatments for PTSD.

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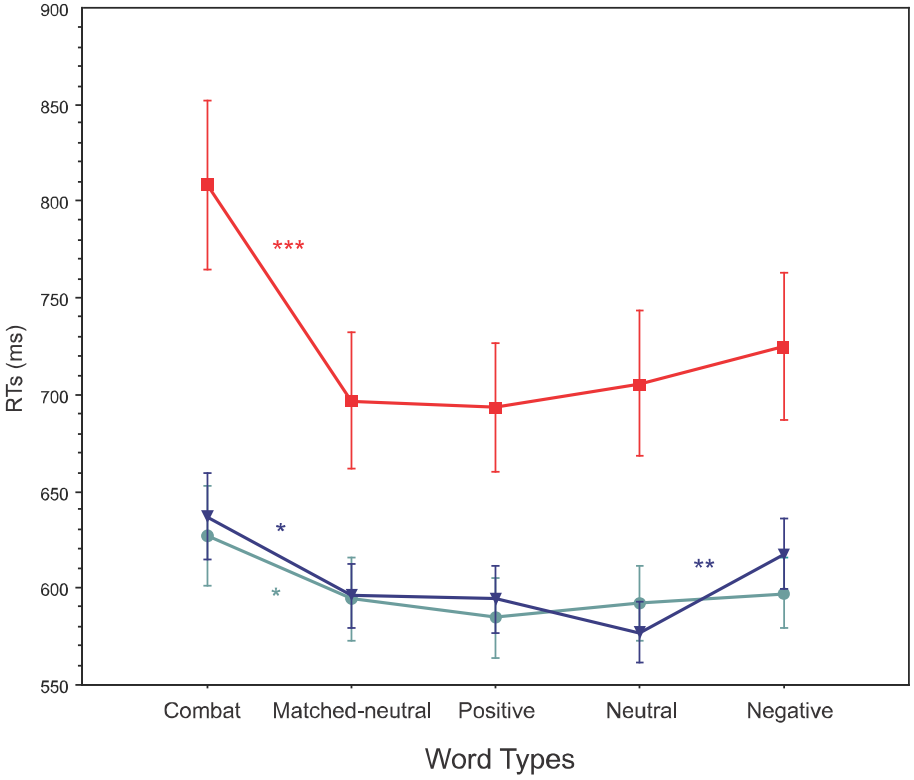
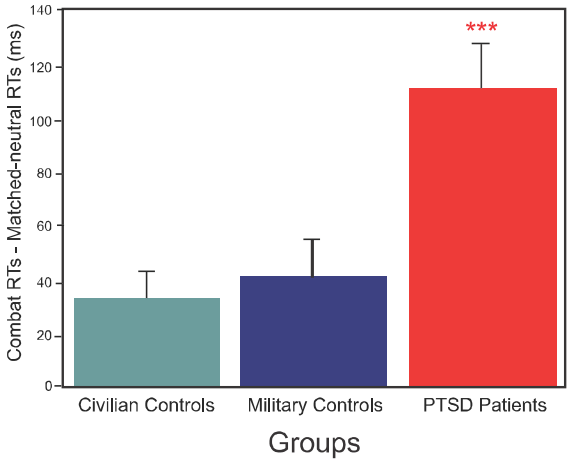
## Figure Legends

Figure 1 – Left: Reaction times for all blocks of word types. Error bars depict standard errors. Right: Mean Stroop interference scores (Combat RTs minus Matched-neutral RTs). Error bars depict standard errors.

Figure 2 – Left: Mean reaction times for Combat (solid lines) and Matched-neutral (dashed lines) blocks across quarters. Error bars depict standard errors. Right: Mean Stroop interference scores across quarters (Combat RTs minus Matched-neutral RTs). Error bars depict standard errors.

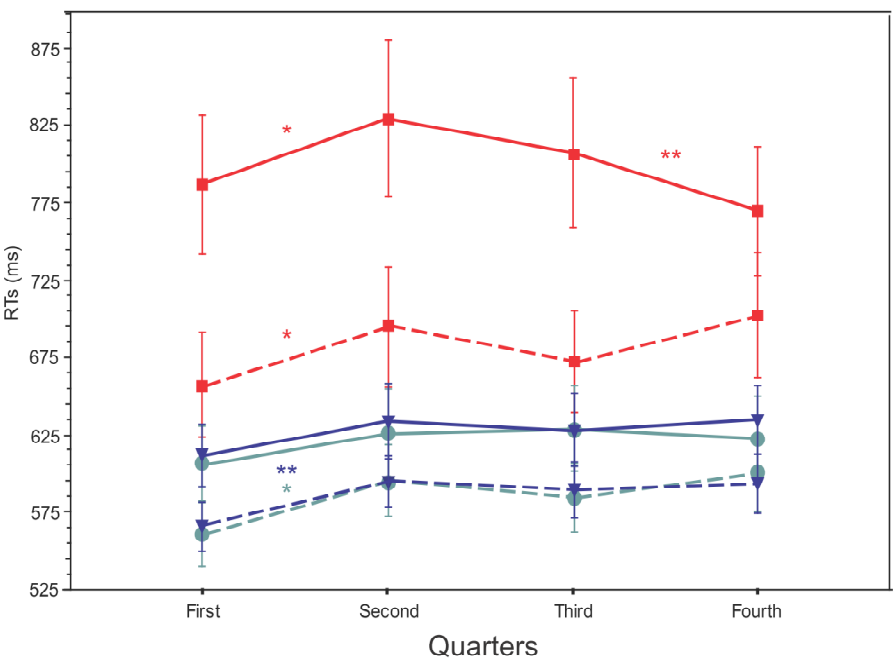


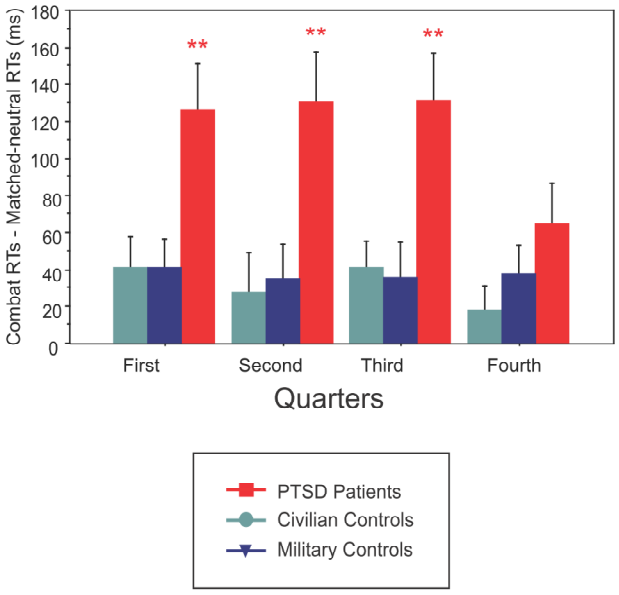





*Note:* * = p<.05, ** = p<.01, *** = p<.001

Figure 1




*Note: * = p<.05, ** = p<.01, *** = p<.001*

Figure 2

**Additional files provided with this submission:**

Additional file 1: Tables.docx, 20K
http://www.biomedcentral.com/imedia/3563010717570180/supp1.docx
Additional file 2: Appendix.docx, 47K
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Table 1

*Demographic Information and Self-Rating Scores for Patient and Control Groups*

| | PTSD Patients (n=30) | Military Controls (n=30) | Civilian Controls (n=30) |
|---|---|---|---|
| Age (yrs) | 32.3 ± 7.9 (ns) (24-51) | 33.6 ± 8.3 (23-48) | 32.2 ± 8.3 (20-49) |
| Education (yrs) | 13.1 ± 1.5 (***) (8-16) | 14.6 ± 1.7 (12-18) | 14.8 ± 1.8 (12-20) |
| Handedness | 27 R, 2 L, 1 ambi | 26 R, 4 L | 29 R, 1 ambi |
| Deployed (n) | 30 | 19 | --- |
| Combat (n) | 26 | 8 | --- |
| BDI | 19.9 ± 9.3 (***) | 5.5 ± 7.0 | 3.0 ± 3.16 |
| PCL | 57.7 ± 11.9 (***) | 26.5 ± 10.9 | 26.0 ± 9.72 |

*Note.* The mean ± standard deviation and range are given for age and education. n.s. = not significantly different from control groups; *** significantly different from control groups at $p<.001$; R = right, L = left, ambi = ambidextrous; LOC = loss of consciousness (of 30 patients with mTBI, 21 had LOC, 5 did not, and 4 were not sure whether they had LOC); PCL = PTSD checklist; BDI = Beck Depression Inventory.

Table 2

*Summary of Word Type Comparisons by Group*

| Group | Comparison | RT difference | *p* |
|---|---|---|---|
| PTSD Patients | Combat vs Matched-neutral | 112 ms | $p<.0001$ |
| | Negative vs Neutral | 19 ms | $p=.19$ |
| | Positive vs Neutral | 13 ms | $p=.26$ |
| Military controls | Combat vs Matched-neutral | 41 ms | $p=.009$ |
| | Negative vs Neutral | 41 ms | $p=.001$ |
| | Positive vs Neutral | 18 ms | $p=.08$ |
| Civilian Controls | Combat vs Matched-neutral | 33 ms | $p=.01$ |
| | Negative vs Neutral | 5 ms | $p=.61$ |
| | Positive vs Neutral | 7 ms | $p=.41$ |

Table 3

*Stroop Interference Across Block Quarters*

| | PTSD Patients | Military Controls | Civilian Controls |
|---|---|---|---|
| First Quarter | 126.35 ms | 41.66 ms | 41.82 ms |
| Second Quarter | 131.23 ms | 35.18 ms | 27.99 ms |
| Third Quarter | 131.35 ms | 35.89 ms | 41.62 ms |
| Fourth Quarter | 64.36 ms | 38.02 ms | 18.73 ms |

*Note*: Interference reaction times (RT) reflect Combat RT minus Matched-neutral RT.

APPENDIX

Word lists for each category of 84 words each. Combat and Matched-neutral words include general combat words, city names, words unique to OEF/OIF, and abbreviations.

| *Positive* | *Negative* | *Neutral* | *Combat* | *Matched-Neutral* |
|---|---|---|---|---|
| hug | cut | boy | gun | van |
| joy | mad | hay | war | net |
| car | hit | shy | body | city |
| dog | lie | cat | bomb | week |
| eat | sin | bus | kill | move |
| sun | rat | air | tour | ride |
| toy | fat | bed | vest | vine |
| gift | hurt | door | medic | tenor |
| fame | dump | milk | shell | quote |
| cute | foul | dirt | abduct | obsess |
| grin | mold | slow | ambush | gossip |
| idea | rude | silk | Apache | Athena |
| snow | pity | seat | captor | caddie |
| song | jail | foot | combat | bottle |
| star | sick | safe | convoy | pastry |
| heal | lost | lamp | gunmen | sitter |
| baby | tomb | item | gunner | jurors |
| cake | burn | farm | kidnap | peruse |
| cozy | debt | bowl | martyr | dining |
| jolly | trash | bench | mortar | comets |
| proud | crime | rusty | patrol | skiing |
| puppy | slime | habit | sniper | tenant |
| honor | crude | bland | terror | permit |
| humor | slave | salad | weapon | expert |
| brave | roach | metal | airlift | roofing |
| lucky | alone | quart | captive | sunrise |
| music | scorn | plant | execute | examine |
| merry | loser | horse | explode | consume |
| loyal | blind | jelly | gunfire | biscuit |
| treat | snake | wagon | hostage | seniors |
| learn | dirty | slush | infidel | puritan |
| loved | filth | table | militia | antenna |
| silly | stink | sleep | missile | founder |
| truth | drown | chair | severed | resumed |

| child | thief | bored | suicide | faculty |
|---|---|---|---|---|
| cheer | fever | board | torture | thunder |
| glory | fraud | elbow | trigger | housing |
| champ | flood | tower | warfare | booklet |
| palace | malice | pencil | wounded | rounded |
| dollar | broken | solemn | amputate | renovate |
| dancer | wicked | poster | casualty | tapestry |
| strong | misery | violin | evacuate | unifying |
| travel | offend | square | militant | partisan |
| comedy | rotten | window | prisoner | observer |
| dinner | stupid | sphere | roadside | newsroom |
| savior | horror | gentle | shrapnel | trustees |
| mother | crisis | golfer | blindfold | blueprint |
| riches | hatred | moment | crossfire | staircase |
| bright | damage | butter | explosive | undefined |
| talent | rabies | engine | insurgent | condiment |
| joyful | poison | finger | checkpoint | paintbrush |
| trophy | insane | museum | concussion | complexion |
| honest | insult | basket | decapitate | redecorate |
| scholar | selfish | obesity | projectile | dishwasher |
| admired | tragedy | comfort | Anbar | Cairo |
| sunrise | trouble | packets | Basra | Paris |
| festive | useless | cottage | Kabul | Delhi |
| holiday | tornado | cabinet | Mosul | Milan |
| hopeful | garbage | staples | Bagram | Lisbon |
| fantasy | lawsuit | staying | Kirkuk | Moscow |
| devoted | delayed | symbols | Baghdad | Bristol |
| diamond | illness | cabbage | Falluja | Jakarta |
| victory | corrupt | shorter | Haditha | Nairobi |
| justice | outrage | retired | Kandahar | Damascus |
| liberty | destroy | arrange | caves | trunk |
| magical | divorce | history | behead | bestow |
| blossom | penalty | mixture | Mullah | Bishop |
| improve | poverty | relaxed | Muqtada | Juanita |
| adorable | disaster | bathroom | Taliban | Chianti |
| terrific | bankrupt | building | warlord | shipman |
| vacation | arrogant | umbrella | Zarqawi | Audubon |
| treasure | troubled | thorough | detainee | detective |
| inspired | contempt | windmill | firefight | fieldwork |
| laughter | confused | feathers | Kalashnikov | Appalachians |
| luscious | terrible | periodic | HV | UV |

| | | | | |
|---|---|---|---|---|
| exercise | pressure | reserved | RPG | DVD |
| friendly | jealousy | performs | IED | DNA |
| champion | rejected | pamphlet | WMD | NBA |
| sapphire | ridicule | neighbor | APC | NFL |
| applause | sickness | corridor | CHU | PDA |
| ambition | starving | spinning | MOUT | RSVP |
| outdoors | dreadful | curtains | AK-47 | BLVD |
| pleasure | insecure | segments | KMTC | USPS |
| prestige | helpless | cylinder | VBIED | SCUBA |

*Note:* OEF/OIF = Operation Enduring Freedom / Operation Iraqi Freedom.

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# Impaired Response Inhibition in Veterans with Post-Traumatic Stress Disorder and Mild Traumatic Brain Injury

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**Abstract**

Combat veterans with post-traumatic stress disorder (PTSD) can show impairments in executive control and increases in impulsivity. The current study examined the effects of PTSD on motor response inhibition, a key cognitive control function. A Go/NoGo task was administered to veterans with a diagnosis of PTSD based on semi-structured clinical interview using DSM-IV criteria ($n = 40$) and age-matched control veterans ($n = 33$). Participants also completed questionnaires to assess self-reported levels of PTSD and depressive symptoms. Performance measures from the patients (error rates and reaction times) were compared to those from controls. PTSD patients showed a significant deficit in response inhibition, committing more errors on NoGo trials than controls. Higher levels of PTSD and depressive symptoms were associated with higher error rates. Of the three symptom clusters, re-experiencing was the strongest predictor of performance. Because the co-morbidity of mild traumatic brain injury (mTBI) and PTSD was high in this population, secondary analyses compared veterans with PTSD+mTBI ($n = 30$) to veterans with PTSD only ($n = 10$). Although preliminary, results indicated the two patient groups did not differ on any measure ($p > .88$). Since cognitive impairments could hinder the effectiveness of standard PTSD therapies, incorporating treatments that strengthen executive functions might be considered in the future. (*JINS*, 2012, *18*, 1–10)

**Keywords:** PTSD, TBI, Go/NoGo, Executive control, Inhibitory control, Impulsivity

## INTRODUCTION

Post-traumatic stress disorder (PTSD) and traumatic brain injuries (TBI) can have detrimental effects on the cognitive and emotional functioning of U.S. veterans returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Impairments in executive control functions are frequently observed in this population (Vasterling, Verfaellie, & Sullivan, 2009). Although the effects of PTSD on executive functions have not received as much attention as the well-documented changes in memory and fear learning, many studies have found that impairments do occur (Koso & Hansen, 2006; Leskin & White, 2007; Vasterling, Brailey, Constans, & Sutker, 1998). Recent reviews have suggested that deficits in attention and executive control can be evident even when the experimental stimuli are emotionally neutral, as opposed to trauma-related (Vasterling & Verfaellie, 2009; Vasterling et al., 2009; Qureshi et al., 2011). Subtle impairments in executive function could hinder the effectiveness of PTSD treatments that rely on the retrieval of autobiographical memories and cognitive reappraisal techniques, such as prolonged exposure and cognitive processing therapy (Vasterling & Verfaellie, 2009). Furthermore, executive control over thought and behavior is necessary for effective disengagement from an overwhelming preoccupation with traumatic stimuli (Aupperle, Melrose, Stein, & Paulus, 2012).

The lateral prefrontal cortex (PFC) is thought to implement cognitive control by exerting top-down influences over sensory and motor processing (Miller & Cohen, 2001). In addition, the anterior cingulate cortex (ACC) has been implicated in a variety of cognitive tasks that require executive control processes (Botvinick, Cohen, & Carter, 2004; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Swick & Turken, 2002). Response inhibition, or the ability to inhibit prepotent responses, is thought to rely on the integrity of specific regions in the lateral and medial PFC

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(Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Picton et al., 2007; Swick, Ashley, & Turken, 2008). It is a core executive control function that has been dissociated from other higher cognitive processes such as task switching and working memory updating (McNab et al., 2008; Miyake et al., 2000; Nee, Wager, & Jonides, 2007). In PTSD, functional alterations have been observed in the ACC and other medial frontal regions (Etkin & Wager, 2007; Shin, Rauch, & Pitman, 2006), as well as in lateral PFC (Morey, Petty, Cooper, Labar, & McCarthy, 2008). These alterations could account for some of the observed deficits in emotion regulation and inhibitory control functions.

The Go/NoGo (GNG) task has been used extensively to assess response inhibition in both animals (Petrides, 1986) and humans (Swick, Ashley, & Turken, 2011). In this task, a motor response is given to one stimulus class and withheld to another. The NoGo stimuli are typically infrequent to establish a prepotent tendency to respond. Impairments in the GNG task have been observed in clinical populations with inhibitory deficits, such as attention deficit hyperactivity disorder (ADHD), substance abuse, schizophrenia, and borderline personality disorder (Chambers, Garavan, & Bellgrove, 2009; Donohoe et al., 2006; Fisher, Aharon-Peretz, & Pratt, 2011; Rentrop et al., 2008). These disorders are thought to involve dysfunctions of frontal inhibitory processes, which can lead to increases in impulsive behavior. In line with these observations, a recent meta-analysis of 48 GNG imaging studies in controls revealed that two major foci of activation included the right middle frontal gyrus (MFG) and the ACC/pre-supplementary motor area (pre-SMA) region (Swick et al., 2011). Both of these frontal areas have been implicated in PTSD. Indeed, a group of civilian participants with PTSD showed an increase in false alarm errors in a GNG task and reduced activation in these same regions, relative to controls (Falconer et al., 2008).

The OEF/OIF patient population differs from many other populations because PTSD and mild TBI (mTBI) frequently co-occur. The estimated prevalence of this co-morbidity has ranged from 33% to 39% in the largest studies of OEF/OIF veterans (Carlson et al., 2011). Therefore, it is important to determine the extent of inhibitory control deficits in these patients, who are at increased risk for substance abuse and other impulsive behaviors (Jakupcak et al., 2009).

Studies in civilians with mTBI commonly observe executive dysfunction and memory impairments (Mathias, Beall, & Bigler, 2004), although these deficits tend to resolve within one to three months (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). There is considerable disagreement, however, in the characterization of mTBI as a minor contributor to post-deployment problems in OEF/OIF veterans (Sigford, Cifu, & Vanderploeg, 2009). Nonetheless, the overlap with PTSD symptoms is extensive (Stein & McAllister, 2009), and disentangling the effects of each has been challenging. It is becoming increasingly apparent that PTSD makes a substantial contribution to the persistent post-concussive symptoms (PCS) reported by OEF/OIF veterans (Hoge et al., 2008). In one recent study of 339 OEF/OIF veterans with positive mTBI histories, PTSD symptoms uniquely accounted for 46.6% of the variance in self-reported PCS, while loss of consciousness accounted for only 1.6% (Lippa, Pastorek, Benge, & Thornton, 2010).

The cumulative impact of mTBI and PTSD on neurocognitive function has not been extensively explored in soldiers who have served in OEF and OIF, who are typically exposed to chronic stressors and threats to safety. Previous neuropsychological results in this population using standardized tests have been mixed, with some reporting deficits (Marx et al., 2009; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009) while others have not (Brenner et al., 2010; Gordon, Fitzpatrick, & Hilsabeck, 2011). However, no study has yet examined response inhibition in OEF/OIF veterans with mTBI and PTSD using the sensitive GNG task.

The current experiment tested veterans with PTSD and mTBI primarily due to blast injury, and veterans with PTSD only. Because our population had a paucity of OEF/OIF veterans with TBI but without PTSD, these individuals were excluded. Determining the effects of PTSD and mTBI on inhibitory control functions is critical to providing appropriate cognitive therapies and rehabilitation programs. After returning from Iraq and Afghanistan, many veterans face difficulties returning to work and maintaining relationships, even if deficits on standardized neuropsychological tests are not observed. Therefore, the development of more sensitive experimental designs is critical in evaluating potential tendencies toward impulsive behaviors.

The major question posed by the present study was whether OEF/OIF veterans with PTSD would show impairments in motor response inhibition. False alarm errors on NoGo trials were used as the primary measure of inhibitory control abilities. To manipulate the prepotency of responding, and hence the need for inhibitory control, the probability of Go to NoGo stimuli alternated between 50/50 (“easy”) and 90/10 (“difficult”) in different blocks. If the function of lateral and medial PFC regions is altered in the patients, one might predict that their performance in the GNG task would be impaired. Although the majority of patients (75%) had both PTSD and mTBI, a secondary question was whether the presence of a mild TBI would result in further deficits in those with PTSD.

Participants also completed standardized questionnaires to assess the severity of PTSD and depressive symptoms. We predicted that response inhibition performance would be related to scores on the PTSD checklist (PCL), with higher error rates in those with higher PCL scores. If the addition of a mild TBI is associated with a further decline in inhibitory control, then the combination of blast-related mTBI with PTSD could ultimately hinder recovery, from both the post-concussive symptoms and the psychiatric sequelae.

## METHODS

### Participants

The participants were 40 combat veterans diagnosed with PTSD (39 male, 1 female) and 33 age-matched veteran

**Table 1.** Demographic information and self-rating scores for the PTSD patients, the patient subgroups with and without mTBI, and the controls

| | Patients ($n = 40$) | PTSD+mTBI ($n = 30$) | PTSD only ($n = 10$) | Controls ($n = 33$) |
|---|---|---|---|---|
| Age (yrs) | 32.6 ± 7.5 (n.s.) | 32.3 ± 7.5 | 32.6 ± 7.6 | 33.4 ± 8.1 |
| Education (yrs) | 13.3 ± 1.4 (***) | 13.6 ± 1.2 | 13.2 ± 1.5 | 14.6 ± 1.6 |
| Handedness | 35 R, 3 L, 2 ambi | 25 R, 3 L, 2 ambi | 10 R | 30 R, 3 L |
| Deployed (*n*) | 40 | 30 | 10 | 19 |
| Combat (*n*) | 40 | 30 | 10 | 8 |
| TBI events (*n*) | 9 one, 21 > one | 9 one, 21 > one | – | – |
| Type of injury | 27 blast or both 3 nonblast | 27 blast or both 3 nonblast | – | – |
| LOC | 21; 5 dazed, 4 uncertain | 21; 5 dazed, 4 uncertain | – | – |
| Years post | 3.9 ± 1.6 | 3.8 ± 1.5 | 4.0 ± 2.2 | – |
| Medications (*n*) | 23 | 18 | 5 | 2 |
| PCL-M | 58.7 ± 12.1 (***) | 59.4 ± 11.2 | 56.5 ± 14.9 | 27.3 ± 11.0 |
| BDI | 20.6 ± 9.9 (***) | 20.0 ± 12.3 | 20.8 ± 9.2 | 6.1 ± 7.1 |

*Note.* The mean ± standard deviation are given for age, education, estimated years post-event(s), PCL-M, and BDI. The patient subgroups did not differ from each other for age, education, years post-event, PCL-M, and BDI.
n.s. = not significantly different from controls; *** Significantly different from controls at $p < .001$.
R = right; L = left; ambi = ambidextrous; LOC = loss of consciousness (of 30 patients with mTBI, 21 had LOC, 5 did not, and 4 were not sure whether they had LOC); Medications = number on psychoactive medications; PCL-M = post-traumatic stress disorder checklist, military version; BDI = Beck Depression Inventory; mTBI = mild traumatic brain injury.

controls (31 male, 2 female). Among the PTSD patients, 30 had sustained one or more mTBIs (primarily due to blast injury while serving in the military), while 10 had no history of mTBI (see Table 1 for details). Participants with evidence of significant medical disease, severe psychiatric problems (such as schizophrenia or bipolar disorder), active substance abuse, visual deficits, or history of other neurological events were excluded. Another 6 participants (4 patients, 2 controls) were initially enrolled, then excluded when additional information was revealed (childhood TBI; non-military PTSD; moderate TBI; other psychiatric disorder; not OEF/OIF). Most of the patients were identified and diagnosed in the TBI clinic of the consulting neurologist. A semi-structured clinical interview was conducted, and mild TBI was diagnosed based on patient self-report of the following criteria from the VA/DoD Clinical Practice Guidelines—loss of consciousness (LOC) 30 min or less or altered mental status (e.g., feeling dazed, disoriented, or confused), with post-traumatic amnesia less than 24 hr (The Management of Concussion/mTBI Working Group, 2009). PTSD diagnosis was based on semi-structured clinical interview using DSM-IV criteria. The diagnoses of mTBI and PTSD were corroborated with available VA medical records, to the fullest extent possible.

The diagnosis of PTSD was based on a review of the VA's Computerized Patient Record System (CPRS) for each enrolled patient. The initial PTSD diagnosis was made when the veteran sought help through the VA. The majority (36 of 40) were diagnosed by VA mental health providers. The presence of PTSD was confirmed by the consulting neurologist in 10 of these 36 patients upon entry into the study. One patient was diagnosed solely by the neurologist, and 3 patients were not enrolled in the VA system. A small number of participants were recruited from the local Vet Center, which provides services for PTSD but does not share diagnostic information with the VA.

Controls were recruited primarily through advertisements. Potential control subjects were screened for exclusionary criteria (described above) and history of mTBI or PTSD through an initial telephone interview, and further assessed at the first visit. Demographic information is shown in Table 1. The groups were matched for age but not education level. This could be due to the inability of many of the patients to return to school after their military service, and is typical of earlier studies on veterans with PTSD (e.g., McNally, Kaspi, Riemann, & Zeitlin, 1990; Vrana et al., 1995). However, another possibility is that low education serves as a risk factor for developing PTSD (Iversen et al., 2008; Larson, Booth-Kewley, Highfill-McRoy, & Young, 2009); thus, those with lower educational attainment were at greater risk for PTSD. Level of education did not influence the outcome, however, as will be discussed in the Results section.

Wechsler Test of Adult Reading (WTAR) data (Wechsler, 2001) were available for a subset of the participants (14 patients and 17 controls). The estimated full-scale IQ (FSIQ) did not differ between the groups [$t(1,29) = 1.44$; $p = .16$], who were well-matched and representative of the entire sample (Table 2).

English was the primary language for all participants. The subjects signed informed consent statements approved by the Institutional Review Board of the VA Northern California Health Care System and were paid for their participation. All procedures were in compliance with the Declaration of Helsinki.

## Go-NoGo Task

We implemented the experimental design used in a previous study on patients with frontal lobe lesions (Swick et al., 2008). Stimuli consisted of single uppercase letters printed in a large black font (248 pt) on a white background. The stimuli

**Table 2.** Demographic information, self-rating scores, estimated full-scale IQ based on Wechsler Test of Adult Reading (WTAR) scores, and NoGo errors in the GNG task for a subset of the participants

| | Patients ($n = 14$) | Controls ($n = 17$) |
|---|---|---|
| Age (yrs) | 36.0 ± 8.5 (n.s.) | 35.2 ± 8.8 |
| Education (yrs) | 13.8 ± 1.2 (n.s.) | 14.6 ± 2.0 |
| PCL-M | 57.0 ± 13.0 (***) | 27.9 ± 10.0 |
| BDI | 20.4 ± 8.6 (***) | 5.4 ± 5.4 |
| FSIQ (est.) | 101.6 ± 11.1 (n.s.) | 106.8 ± 9.2 |
| 50/50 errors | 14.0 ± 8.6 (***) | 6.1 ± 3.2 |
| 90/10 errors | 45.9 ± 17.4 (***) | 22.9 ± 12.2 |

*Note.* The mean ± standard deviation are given for age, education, PCL-M, and BDI. n.s. = not significantly different from controls; *** significantly different from controls at $p \leq .001$.
PCL-M = post-traumatic stress disorder checklist, military version; BDI = Beck Depression Inventory; GNG = Go/NoGo task; FSIQ = full-scale IQ.

were presented on a 16 inch ViewSonic monitor using a PC that ran Presentation® software (Neurobehavioral Systems, Inc., http://www.neurobs.com/). Stimuli were rapidly and serially presented at the center of a computer screen for 200 ms duration once every 1500 ms. Subjects were instructed to respond as quickly as possible to every letter except for "X" by pressing a button on the keyboard with the index finger of the dominant hand. In four separate blocks of trials, the proportion of "Go" to "NoGo" trials alternated between 50/50 and 90/10. There were 140 trials per block, with short rest breaks between each block. A short practice set of 30 trials (15 Go and 15 NoGo, randomly intermixed) preceded the experimental trials.

## Questionnaires

At the end of the session, all subjects completed three self-report questionnaires: the Barratt Impulsiveness Scale (BIS), the PTSD Checklist, Military Version (PCL-M), and the Beck Depression Inventory (BDI). The BIS is a 30-item self-report measure thought to assess the personality construct of "impulsiveness" (Patton, Stanford, & Barratt, 1995). Results from the BIS will be reported in a separate publication. The PCL-M for DSM-IV (Weathers, Litz, Huska, & Keane, 1994) is an accepted diagnostic tool for measuring PTSD (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). The PCL-M is a 17-item self-report tool that establishes the presence and degree of PTSD symptoms in military personnel. It has three clusters or subsets: re-experiencing, numbing, and hyperarousal. PTSD is indicated in a veteran population with a score of 50 or greater (Forbes, Creamer, & Biddle, 2001). The PCL-M score of one control participant who had not yet sought clinical care placed them in the PTSD group. This individual was subsequently diagnosed with PTSD by a psychiatrist. Another veteran recruited *via* an advertisement initially self-identified as having PTSD but had a low score on the PCL-M. Omitting these two individuals did not affect the results, so they are included in all analyses. In addition, a clinical neuropsychologist reviewed information from both patients and determined that their PCL scores reflected current symptomotology (or lack thereof). The BDI is one of the most commonly used self-report screens for major depressive disorder (MDD) and has been validated with well-established psychometric properties (Beck, Steer, & Gabin, 1988). The BDI is a 21-item test which measures the presence and degree of depression in adolescents and adults.

## Data Analysis

Error data were characterized as missed responses to Go stimuli and false alarm responses to NoGo stimuli. The mean reaction time (RT) was calculated for each subject and sorted into correct responses to Go stimuli and incorrect responses to NoGo stimuli. Statistical analyses were carried out using repeated measures analyses of variance (ANOVAs) with factors of group (patients, controls) and probability (50/50, 90/10). Secondary analyses compared patients with mTBI and PTSD to those with PTSD only. The correlations between self-report measures and errors in the difficult 90/10 condition were determined using the Spearman rank-order statistic, with a Bonferroni correction for multiple comparisons ($p < .005$). Effect sizes are reported as partial eta-squared ($\eta_p^2$) for ANOVA and Cohen's $d$ for follow-up comparisons.

# RESULTS

## Accuracy

An initial ANOVA with factors of group (controls, patients), probability (50/50, 90/10), and error type (misses, false alarms) revealed that every main effect and interaction was highly significant, including group × error type [$F(1,71) = 26.11$; $p < .0001$; $\eta_p^2 = .26$]. Thus, separate ANOVAs were performed for errors of omission on Go trials (misses) and errors of commission on NoGo trials (false alarms). In general, the rate of misses was very low and did not differ by probability ($p = .19$). The percentage of missed responses for the 50/50 and 90/10 probability conditions was 0.65% and 0.28%, respectively, for controls; and 1.93% and 1.55% for patients. Although floor effects are a concern, the percentage of misses was greater in the patients than in controls [$F(1,71) = 5.20$; $p = .03$; $\eta_p^2 = .07$], which did not interact with probability ($p > .9$).

In contrast, NoGo errors (Figure 1, top) showed a highly significant effect of group [$F(1,71) = 26.44$; $p < .0001$; $\eta_p^2 = .27$], probability [$F(1,71) = 93.97$; $p < .0001$; $\eta_p^2 = .73$], and an interaction between the two [$F(1,71) = 14.03$; $p = .0004$; $\eta_p^2 = .17$]. The PTSD patients made more false alarm errors than controls for both the 50/50 [$F(1,71) = 22.83$; $p < .0001$; $d = 1.12$] and the 90/10 [$F(1,71) = 23.35$; $p < .0001$; $d = 1.14$] probability conditions. Although the effect sizes are nearly

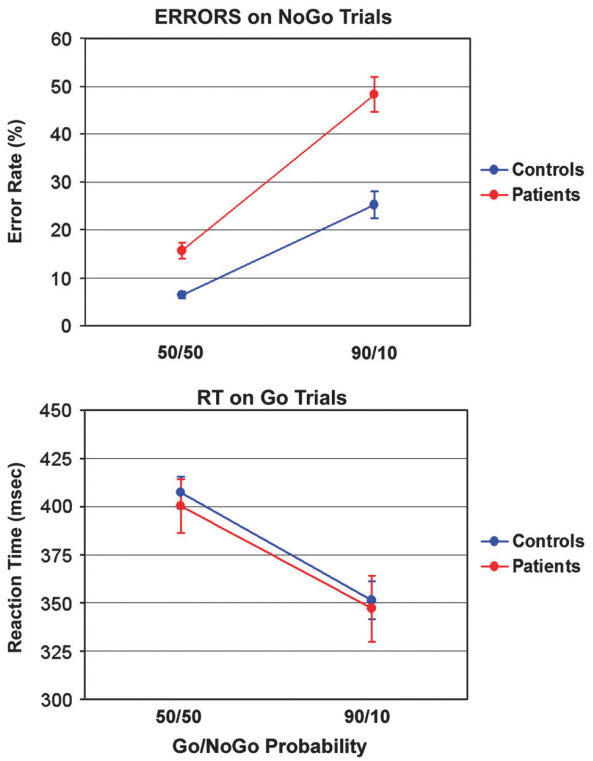


**Fig. 1. Top:** False alarm errors (percentage of NoGo errors) for the patients ($n = 40$) and controls ($n = 33$) in the easy (50/50) and difficult (90/10) conditions. **Bottom:** Reaction times (RTs) on correct Go trials (in milliseconds) in the easy (50/50) and difficult (90/10) conditions. The error bars depict standard errors.

equivalent, the significant interaction suggests the patients' difficulty with inhibiting inappropriate responses was exacerbated in the difficult 90/10 condition, when responding was prepotent. A secondary ANOVA was conducted to compare PTSD patients with and without mTBI (Figure 2), revealing that patients with both PTSD and mTBI did not differ from those with PTSD only. The main effect of group [$F(1,38) = 0.2$; $p = .89$] and the group by probability interaction [$F(1,38) = 0.2$; $p = .88$] were not significant.

## Reaction Times

The initial comparison examined RTs on correct Go trials only (Figure 1, bottom), and revealed no differences between the patients and controls in the speed of responding ($p > .7$). All subjects were faster to respond to targets in the 90/10 condition than in the 50/50 condition, which was reflected in a highly significant main effect of probability [$F(1,71) = 200.59$; $p < .0001$]. Probability did not interact with group ($p > .7$). The secondary analysis showed that patients with both PTSD and mTBI did not differ from those with PTSD only ($p > .7$).

An additional ANOVA compared response times for correct and error trials. All participants had faster RTs on incorrect NoGo trials (308 ms ± 70 ms) than on correct

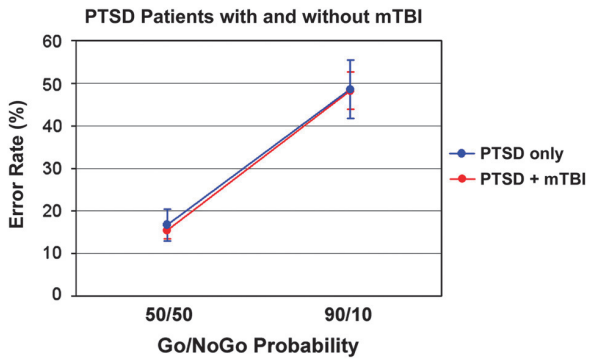


**Fig. 2.** False alarm errors (percentage of NoGo errors) for patients with both mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD; $n = 30$) and patients with PTSD only ($n = 10$) in the easy (50/50) and difficult (90/10) conditions. The error bars depict standard errors.

Go trials (376 ms ± 86 ms), suggesting that impulsive responding led to the majority of errors in performance. This result was indicated by a main effect of accuracy [$F(1,70) = 479.30$; $p < .0001$][1] that did not interact with group ($p > .3$). This speeding up on error trials was numerically greater for the 50/50 condition (80 ms) than for the 90/10 condition (57 ms), as indicated by the probability by accuracy interaction [$F(1,70) = 11.28$; $p = .001$].

## Correlations Between Experimental and Self-Report Measures

The associations between scores on the self-report questionnaires and false alarm errors in the difficult 90/10 condition were determined using Spearman Rank Correlations (corrected at $p < .005$). Scores on the PCL-M and BDI showed a strong correlation with performance: more severe levels of PTSD symptoms (rho = .52; $p = .0001$) and depression (rho = .53; $p < .0001$) were both associated with higher error rates. All three PTSD symptom clusters produced a correlation with error rates: re-experiencing (rho = .54; $p < .0001$), avoidance/numbing (rho = .47; $p < .0001$), and hyperarousal (rho = .49; $p < .0001$). However, when these three variables were entered into a standard multiple regression analysis to control for shared variance (see Vasterling et al., 1998), re-experiencing was the only significant predictor of errors in the 90/10 condition ($p = .02$; see Table 3). Finally, a striking correlation between PCL-M and BDI scores was observed (rho = .90; $p < .0001$), indicating that PTSD and depression symptoms showed a high level of co-morbidity in these OEF/OIF veterans. As clearly expected based on clinician diagnosis, the patients reported higher PCL-M and BDI scores than the control group, but there were no differences between PTSD patients with and without mTBI (Table 1).

[1] There is one less degree of freedom in the denominator because one control subject did not have any errors in the 90/10 condition.

**Table 3.** Relationship of false alarm errors in the 90/10 condition to the three PTSD symptom clusters, based on self-reported PCL-M scores

| Symptom cluster | B | Std. Error | β | *t* | *p* |
|---|---|---|---|---|---|
| Re-experiencing | 1.822 | .748 | .478 | 2.435 | .018 |
| Avoidance/numbing | −.131 | .586 | −.048 | −.224 | .823 |
| Hyperarousal | .487 | .787 | .135 | .619 | .538 |

*Note.* $R = .557$; Adjusted $R^2 = .281$; $F(3,69) = 10.36$, $p < .0001$.
PTSD = post-traumatic stress disorder; PCL-M = post-traumatic stress disorder checklist, military version.

## Effects of Education, Estimated IQ, Diagnostic Certainty, and Medications

Two additional analyses established that the patients' deficits in accuracy were unrelated to education level. In the first, the less educated half of the control group ($n = 17$) was compared to the entire patient group (now matched for education: 13.4 *vs.* 13.3 years, respectively). The same results for false alarm errors were obtained: a main effect of group [$F(1,55) = 14.27$; $p = .0004$], and an interaction between group and probability [$F(1,55) = 6.72$; $p = .01$]. In the second, the groups were more closely matched in number. We compared the lower educated half of controls ($n = 17$) to the upper half of patients ($n = 20$), so now the patients were significantly more educated (13.4 *vs.* 14.3 years, respectively; $p = .001$). Again, the same impairment was observed in the patients: a main effect of group [$F(1,35) = 14.01$; $p = .0007$], and an interaction between group and probability [$F(1,35) = 7.55$; $p = .009$].

Thus, group differences in education level did not influence the outcome. Another question is whether there were group differences in IQ which might have affected the results. WTAR data were available for a subset of the participants to provide an estimate of pre-morbid IQ (Wechsler, 2001). As reported previously, the estimated FSIQ did not differ between the groups, who were well-matched and representative of the entire sample (Table 2). This subset of patients made significantly more false alarm errors than controls for both the 50/50 and 90/10 conditions ($p$'s $\leq .001$). Furthermore, errors on the 90/10 condition were not at all correlated with estimated FSIQ ($r = .017$; $p = .92$).

Although the PCL-M was not used for diagnostic purposes, eight patients with a formal diagnosis of PTSD from semi-structured clinical interview had scores below 50 (range, 31–49) on the day they were tested. Removing these patients and any other clinically discrepant participants from the analyses did not affect the results ($p$'s $\leq .0001$ for false alarm errors in both the 50/50 and 90/10 conditions), nor did it change group demographics (mean age for all 40 patients = 32.6 years and for 32 patients = 32.6 years; mean education for all 40 patients = 13.3 years and for 32 patients = 13.1 years).

To examine the effects of prescription drugs on performance, the 23 patients taking psychotropic medication(s) of any class (sedative/hypnotics, antidepressants, mood stabilizers, atypical antipsychotics, opioids, or alpha adrenergic blockers) were compared to the 17 patients who were not. Medication use did not affect RTs (main effect $p = .20$ and interaction $p = .11$, with the trend being faster RTs in those taking medications) or NoGo error rate (main effect $p = .28$ and interaction $p = .31$).

## Role of Deployment, Loss of Consciousness, and Number of Events

Among the veterans in the control group, 19 of 33 were deployed. An additional ANOVA compared these deployed controls ($n = 19$) to the patients ($n = 40$) for NoGo errors. Results were similar to the main analysis: a highly significant effect of group [$F(1,57) = 14.13$; $p = .0004$] and a group by probability interaction [$F(1,57) = 6.56$; $p = .01$] were observed.

As stated earlier, the secondary analysis comparing PTSD patients with and without mTBI found no differences in performance. However, the definition of mTBI includes individuals with altered mental status but no loss of consciousness (LOC). Self-reported LOC occurred in 21 of 30 patients with mTBI. To examine whether PTSD+mTBI patients with self-reported LOC ($n = 21$) might differ from those with PTSD only ($n = 10$), another ANOVA was run. Again, there were no significant main or interactive effects of group (both $p$'s $> .9$). Finally, the group with mTBI was restricted further to those with both LOC and more than two events ($n = 15$), and compared to the PTSD only group. These two patient subgroups did not differ significantly in their PCL-M scores (59.1 *vs.* 56.6 respectively; $p = .62$). There were still no differences for NoGo errors (main effect of group, $p > .9$; interaction: $p > .8$).

## DISCUSSION

The present study demonstrated that OEF/OIF veterans with PTSD were impaired at inhibiting inappropriate motor responses. A speed-accuracy trade-off could not account for this result, as RTs in the patient and control groups were virtually identical. As well, the severity of PTSD and depressive symptoms were both highly correlated with performance. These results suggest that response inhibition is compromised in participants with PTSD, which is consistent with previous results in civilians (Falconer et al., 2008; Wu et al., 2010) and Gulf War veterans (Vasterling et al., 1998). A deficit in inhibitory control could have detrimental effects on daily activities such as driving (Lew, Amick, Kraft, Stein, & Cifu, 2010), and may hinder recovery from traumatic events (Aupperle et al., 2012).

In addition, the inhibitory control deficit occurred whether or not the patient had reported a mild TBI in addition to PTSD. Although this finding is preliminary, the fact that mTBI did not add to the cognitive deficits seen in those with PTSD suggests that in the current population, where loss of consciousness was brief (less than 1–2 min in most patients) and where no clear LOC occurred in 30% (with dazed/altered mental status),

PTSD was the primary driver of performance. Further restriction of the mTBI group to those with self-reported LOC and more than two events did not alter this outcome. Furthermore, the severity of PTSD symptoms did not differ in patients with and without mTBI, in agreement with Romesser and colleagues (2011). There has been considerable controversy over the diagnosis of mTBI in OEF/OIF veterans, with some questioning the impact of mTBI on post-deployment functioning relative to PTSD, depression, and other psychiatric disorders (e.g., Hoge et al., 2008; Hoge, Goldberg, & Castro, 2009). Results could differ in military personnel with more "severe" mTBIs, such as those with a combination of blast injury and secondary head trauma, for example, the group of U.S. military personnel airlifted to Landstuhl Medical Center in Germany (Mac Donald et al., 2011). Those subjects showed evidence of white matter abnormalities on diffusion tensor imaging (DTI) scans.

On a related note, the co-morbidity between PTSD and depression symptoms was striking, with a very high correlation between the severity of self-reported symptoms on the two scales. Although the two disorders share the overlapping construct of negative affect, the symptom cluster of re-experiencing is unique to PTSD (Cloitre, Koenen, Gratz, & Jakupcak, 2002). Increased scores on both the BDI and the PCL-M were strongly associated with a higher percentage of false alarm errors in the difficult condition. All three PTSD symptom clusters (re-experiencing, avoidance/numbing, and hyperarousal) were correlated with performance individually, but when entered into a multiple regression, re-experiencing was the only significant predictor of error rate. This finding replicates Vasterling et al. (1998) and suggests that the symptom cluster most unique to PTSD was specifically related to the decline in inhibitory control.

The strong correlation between PCL-M scores and error rates is in agreement with previous results. Falconer and colleagues (2008) also found a positive correlation between false alarm errors and PTSD severity as measured by the Clinician-Administered PTSD Scale (CAPS). In their imaging study, civilian PTSD patients showed reduced activity in the right lateral PFC and the ACC/pre-SMA regions relative to controls. Furthermore, more severe PTSD symptoms were associated with less activation in bilateral PFC and medial frontal areas in the patients (Falconer et al., 2008). This is in accord with what would be predicted on the basis of meta-analytic studies of the GNG task in controls (Swick et al., 2011), because those regions were uniformly recruited for response inhibition across a large number of experiments. The activation foci showing the greatest overlap across GNG imaging studies included the right anterior insula and right MFG (e.g., Zheng, Oka, Bokura, & Yamaguchi, 2008) and dorsomedial areas such as the SMA, pre-SMA, and ACC (e.g., Li, Huang, Constable, & Sinha, 2006; Mostofsky & Simmonds, 2008). As mentioned previously, individuals with PTSD have smaller ACC volumes (Hamner, Lorberbaum, & George, 1999; Rauch et al., 2003; Woodward et al., 2006). It is now becoming more apparent that dorsolateral PFC function may be compromised in PTSD as well (Aupperle et al., 2012; Simmons & Matthews, 2012). Difficulties in recruiting the MFG during a cognitive task were associated with higher levels of PTSD symptoms (Morey et al., 2008).

Disentangling the effects of mTBI, PTSD, and depression on cognitive performance and brain function has not been a straightforward endeavor. In a structural imaging study of individuals with both PTSD and depression, common areas of volume reduction were located in the PFC (Kroes, Rugg, Whalley, & Brewin, 2011). An fMRI study demonstrated that veterans with both mTBI and MDD showed greater activity in the amygdala, and less activity in dorsolateral PFC, than veterans with mTBI only during an emotional face matching task (Matthews et al., 2011).

Robertson, Manly, Andrade, Baddeley, and Yiend (1997) have argued that in addition to motor response inhibition, the Go/NoGo task is a measure of sustained attention. Both motor response inhibition and/or lapses of attention can produce high NoGo error rates. In our experiment, the 90/10 blocks might have been more monotonous than the 50/50 blocks, so sustained attention was required to a greater degree in the former. Thus, it is noteworthy that the patients showed substantially elevated false alarm rates in both conditions. In addition, omitted responses on Go trials were not greatly increased (mean of 1.7% in the patients), as might be expected if distractibility and sustained attention had been the primary difficulties. Although a significant difference was observed, this finding should be interpreted with caution because the controls showed a floor effect, with the rate of misses below 1%. Finally, the pattern of RTs on correct Versus incorrect Go trials indicated that errors were due to impulsive responding. Therefore, an inhibitory control deficit remains the best explanation for the patients' performance.

Previous Go/NoGo results in TBI patients with moderate to severe injuries have been mixed, but a recent meta-analysis of 20 response inhibition studies in adults found a moderate effect size (Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011). Although many papers have reported deficits (e.g., Robertson et al., 1997), others have not (Swick et al., 2008; Whyte, Grieb-Neff, Gantz, & Polansky, 2006). Our prior study demonstrated that patients with severe TBIs and large bilateral lesions in the orbitofrontal cortex were not impaired on the GNG task (Swick et al., 2008). On the other hand, stroke patients with focal lesions in the left inferior frontal gyrus and left anterior insula showed a pattern of impairment similar to that reported here (Swick et al., 2008). However, the present group of OIF/OEF veterans had an even greater deficit in motor response inhibition, which can have important implications for daily life. Since performance did not differ in patients with and without mTBI, these results suggest that PTSD symptoms interfere with effective response inhibition.

The present study has several limitations. PTSD was diagnosed by semi-structured clinical interview instead of the CAPS, which is considered the "gold standard" (Blake et al., 1995). Nonetheless, a strong correlation between false alarm errors and PCL-M scores was observed, suggesting a

relationship between inhibitory control deficits and self-reported PTSD symptom severity that was independent of formal diagnosis. Furthermore, there is a very high correlation between the PCL and the CAPS: diagnostic efficiency of the PCL is 0.900 versus the CAPS (Blanchard et al., 1996). The difficult issue of making an accurate mTBI diagnosis pertains to most veterans of OEF/OIF, as it is dependent on recollection and self-report. Medical records from Iraq and Afghanistan were not available for the patients, as they had no medical treatment at the time. Brief losses of consciousness or altered mental status may not always be caused by blast exposure itself, but can be due to acute stress, confusion, or sleep deprivation (Hoge et al., 2009). Nevertheless, all current participants with mTBI were diagnosed by a neurologist.

Other limitations include the fact that the control veterans were not all deployed or exposed to combat. Future studies should attempt to better match the groups on these factors, as deployment and combat exposure may have detrimental effects on their own. However, an analysis restricted to only those controls who were deployed revealed that the patients were still impaired relative to this group. The controls and patients were not matched for years of education, although subgroup analyses convincingly demonstrated this did not affect the pattern of results. Since all patients were highly motivated to participate in the study, we did not believe that effort was an issue. However, we did not use a measure of effort or malingering to verify this. Another difficult issue is separating the effects of PTSD and depressive symptoms on cognitive performance (Cloitre et al., 2002), due to their high co-morbidity in this population. The current study was not designed to address this question. The recruitment and selection of patients was not completely random, but was primarily focused on those who attended a specialty TBI clinic. Additional efforts were made to recruit from mental health clinics and veterans organizations as well. However, there were fewer patients with PTSD only, so the comparisons between this group and the mTBI + PTSD group were low in power. Finally, due to the difficulty of finding patients with pure mTBI in isolation from PTSD, we were not able to include this population in the current study. Inclusion of this group in future studies will allow stronger conclusions about the effects of mTBI on response inhibition.

## CONCLUSIONS

The present results indicated that OEF/OIF veterans with PTSD were impaired at inhibiting motor responses in a Go/NoGo task. The inhibitory control deficit was exacerbated when responding was more prepotent, suggestive of more impulsive responding in the patients. False alarm error rates were strongly correlated with self-reported symptoms of PTSD and depression. Furthermore, the combination of mTBI and PTSD did not result in worse performance than PTSD alone in the present population. Taken together, the current findings suggest that OEF/OIF veterans with PTSD show impairments in response inhibition. Additional studies are needed to verify that these findings are independent of mTBI. Since neurocognitive impairments may hinder the effectiveness of PTSD therapies that rely on cognitive reappraisal and disengagement from traumatic stimuli (Aupperle et al., 2012; Vasterling & Verfaellie, 2009), incorporating treatments that strengthen executive functions might be considered in the future.

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# Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks

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ABSTRACT

Neuroimaging studies have utilized two primary tasks to assess motor response inhibition, a major form of inhibitory control: the Go/NoGo (GNG) task and the Stop-Signal Task (SST). It is unclear, however, whether these two tasks engage identical neural systems. This question is critical because assumptions that both tasks are measuring the same cognitive construct have theoretical and practical implications. Many papers have focused on a right hemisphere dominance for response inhibition, with the inferior frontal gyrus (IFG) and the middle frontal gyrus (MFG) receiving the bulk of attention. Others have emphasized the role of the pre-supplementary motor area (pre-SMA). The current study performed separate quantitative meta-analyses using the Activation Likelihood Estimate (ALE) method to uncover the common and distinctive clusters of activity in GNG and SST. Major common clusters of activation were located in the right anterior insula and the pre-SMA. Insular activation was right hemisphere dominant in GNG but more bilaterally distributed in SST. Differences between the tasks were observed in two major cognitive control networks: (1) the fronto-parietal network that mediates adaptive online control, and (2) the cingulo-opercular network implicated in maintaining task set (Dosenbach et al., 2007) and responding to salient stimuli (Seeley et al., 2007). GNG engaged the fronto-parietal control network to a greater extent than SST, with prominent foci located in the right MFG and right inferior parietal lobule. Conversely, SST engaged the cingulo-opercular control network to a greater extent, with more pronounced activations in the left anterior insula and bilateral thalamus. The present results reveal the anterior insula's importance in response inhibition tasks and confirm the role of the pre-SMA. Furthermore, GNG and SST tasks are not completely identical measures of response inhibition, as they engage overlapping but distinct neural circuits.

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## Introduction

The ability to override an automatic tendency to respond in a given situation, or to stop a response when a rapid change in plan is required, is a core feature of flexible and adaptive behavior (Goldman-Rakic, 1996). Inhibitory control is a key executive function, separable at a cognitive level from other major executive processes (Miyake et al., 2000). Response inhibition has been a popular topic in the neuroimaging literature (reviewed in Mostofsky and Simmonds, 2008; Nakata et al., 2008; Swick et al., 2008), with activations in the lateral prefrontal cortex (PFC) and dorsomedial PFC receiving the focus of attention. Two major tasks (Go/NoGo and Stop-Signal) have been used to assess motor response inhibition, but few studies have systematically compared whether they recruit largely overlapping brain regions (McNab et al., 2008; Rubia et al., 2001; Zheng et al., 2008). This is important because assertions that the NoGo>Go and Stop>Go comparisons are both measuring the same cognitive construct ("suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior")[1] have theoretical and practical implications. From a theoretical perspective, new efforts to develop formal ontologies of cognitive control functions rely on observable indicators, i.e. behavioral performance and brain activation measures obtained from specific tasks (Lenartowicz et al., 2010). The response inhibition construct currently subsumes GNG, SST, and anti-saccade tasks under one heading. Presumably, if these tasks activate non-overlapping brain regions, then they reflect the engagement of different cognitive processes to some degree (Lenartowicz et al., 2010). From a practical standpoint, impaired performance on either of these tasks in patient populations is often taken as an indication of specific PFC abnormalities (Clark et al., 2007) or frontal lobe dysfunction more generally (Barkley et al., 1992; van der Schoot et al., 2000).

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[1] http://www.cognitiveatlas.org/concept/response_inhibition (The Cognitive Atlas).

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In the Go/NoGo (GNG) task, a motor response is made to one stimulus class and withheld to another. The probability of trial types can be manipulated to set the prepotency of responding, so that withholding a response on NoGo trials is more difficult when Go trials are frequent. In the Stop-Signal Task (SST), responses are made on every trial unless a Stop Signal (e.g., a tone) is presented (Logan et al., 1997). The interval between the Go stimulus and the Stop stimulus (Stop-Signal delay) is varied using an adaptive procedure (Verbruggen and Logan, 2008b). Performance is modeled as a "race" between "go" and "stop" processes, and the stop-signal reaction time (SSRT) is calculated as a measure of inhibitory control. Although these two tasks are often treated interchangeably (Aron et al., 2004; Lenartowicz et al., 2010), it is unclear whether they tap the same cognitive processes and neural substrates. Better understanding of the neural systems common to performance in both tasks and those unique to each task will help with the interpretation of extant literature and design of future studies. Furthermore, more precisely delineated network models of response inhibition tasks may have clinical utility in identifying the neural substrates of impulsive behavior associated with developmental and psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), borderline personality disorder, substance abuse, and the manic phase of bipolar disorder.

Several early GNG papers have argued that motor response inhibition is strongly lateralized to the right hemisphere (Garavan et al., 1999; de Zubicaray et al., 2000; Kawashima et al., 1996; Konishi et al., 1998, 1999), particularly right hemisphere regions in dorsolateral PFC and the inferior frontal gyrus (IFG), as expected for an executive control function. However, most of these studies, as well as others that followed (Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001; Wager et al., 2005; Watanabe et al., 2002) did observe activations in bilateral dorsolateral and ventrolateral PFC, as well as the anterior cingulate cortex (ACC) and pre-supplementary motor area (pre-SMA) in medial PFC. Other areas of activation have included inferior parietal cortex and the basal ganglia.

There have been fewer neuroimaging investigations of response inhibition using the SST, although the number is growing. Some have reported predominant activity in the right IFG (Aron and Poldrack, 2006; Aron et al., 2007; Matthews et al., 2005), while others have observed bilateral activations in the IFG (Cai and Leung, 2009; Leung and Cai, 2007; Li et al., 2006b). However, the pre-SMA, rather than the IFG, has been emphasized as the region critical for stopping by some investigators (Chao et al., 2009; Duann et al., 2009; Sharp et al., 2010). Other notable regions have included the striatum (Vink et al., 2005) and a region in the area of the subthalamic nucleus (Aron and Poldrack, 2006). Overall, neuroimaging findings suggest that response inhibition is subserved by a large-scale distributed system of bilateral cortical and subcortical regions, but showing a right hemisphere dominance.

The initial PET and fMRI studies of GNG used block designs, in which blocks consisting of all Go trials were compared to blocks containing both Go and NoGo. Subsequent event-related fMRI investigations directly compared activation on NoGo to that observed on Go trials. Blocked GNG studies might recruit regions involved in maintaining task set across a sustained period, such as the bilateral anterior insula/frontal operculum, dorsal ACC/medial superior frontal gyrus, right middle temporal cortex, and left inferior parietal lobule (Dosenbach et al., 2006). Other variables that can differ across GNG studies include the probability of NoGo stimuli, task difficulty, and stimulus modality. Go and NoGo stimuli are typically in the same modality and often have similar features, in contrast with the modality shift used in common SST designs. Variables that can differ across SST experiments include the probability of Stop trials, modality of the Stop signal, type of stimuli and task used, whether an adjustable staircase procedure was used to determine stop signal delay, and the comparison condition. The behavioral measures differ between the two tasks as well. Performance is evaluated by error rate on NoGo trials, compared to the primary measure of a stop signal RT (although error rate is also obtained in SST). These potential sources of variability point to the importance of studies that combine well-matched versions of the two tasks.

Three papers have specifically compared the activations produced by GNG and SST in the same groups of subjects. Rubia et al. (2001) found that overlapping regions in lateral PFC, medial PFC, and parietal cortices were activated in the two tasks, although the hemispheric dominance differed: GNG showed greater left hemisphere involvement, while SST showed greater right hemisphere involvement. That study administered variants of each task using block designs, which can introduce strategic and task-set effects. Using an event-related design, Zheng et al., 2008 implicated the right middle frontal gyrus (Brodmann Area 46) as the critical region for response inhibition in both tasks. Finally, McNab et al. (2008) administered GNG and SST (as well as flanker interference and working memory tasks) in a within-subject, event-related experiment that controlled for "oddball" probability effects (i.e., NoGo and Stop trials are typically less frequent than Go trials). Specifically, oddball Go events comprised 25% of the trials, equivalent to the percentage of NoGo and Stop trials (standard Go trials comprised the other 50%). Conjunction analysis for NoGo>oddball Go and Stop>oddball Go comparisons revealed common activations in the right inferior (BA 47) and middle (BA 9/46) frontal gyri, and in the left inferior frontal gyrus (BA 47) and left insula. Given the variability in results across these studies, a conclusive answer on the common neural resources used by GNG and SST tasks has not been reached, thereby motivating the meta-analysis presented here.

Looking to other methods for converging evidence, results from the human lesion literature support the predominance of RIFG in the SST. Patients with lesions in RIFG, but not the LIFG, were impaired in this task, showing longer stop-signal times (Aron et al., 2003). However, we recently reported that patients with focal damage in the LIFG and anterior insula showed response inhibition deficits in the GNG task, particularly when responses were more prepotent (90% Go vs. 50% Go probability; Swick et al., 2008). Our finding does not rule out the possibility that RIFG patients would be more impaired, but it does establish that LIFG is a critical region for accurate performance on GNG. Finally, an event-related potential experiment utilized a combined GNG/SST design and found bilateral frontal sources for the NoGo and Stop P300 components, with larger amplitudes for the latter (Enriquez-Geppert et al., 2010).

These differential findings on the importance of LIFG in response inhibition, along with discrepancies in the neuroimaging literature, raise the possibility that response inhibition is not a unitary process and that the two tasks might be tapping different elements of inhibitory control. In fact, one model of response inhibition (Eagle et al., 2008; Schachar et al., 2007) distinguishes between action restraint — inhibition of a motor response before the response has been initiated (GNG), and action cancelation — inhibition of an already initiated motor response (SST). In this view, NoGo trials are like Stop trials where the stop signal occurs with zero delay, so that a strong motor response has not built up by the time the need to stop is realized. However, there is ample evidence for motor preparation on both Go and NoGo trials (Zhang et al., 2008) so to some extent this task can be considered not only in the light of action restraint, but also as a form of action cancelation. This is especially true when the task has a low probability of NoGo trials and a fixed inter-stimulus interval (Levy and Wagner, 2010).

Alternatively, the response inhibition processes utilized in the two tasks might be similar, but other attentional and cognitive control processes are differentially recruited. The literature remains inconclusive, and a search for functional neuroanatomical differences may clarify whether the two tasks are indeed measuring different psychological constructs. Meta-analysis of the functional neuroimaging literature

provides an objective approach to assessing the common and distinct aspects of the neural circuitry associated with performance in different tasks. Recently developed software tools, such as BrainMap (Laird et al., 2005b) allow large sets of imaging findings to be analyzed to discover consistent patterns that might not be evident from a qualitative overview of a limited number of studies. If the neural systems supporting inhibitory control in the Go/NoGo and Stop-Signal tasks are essentially identical, this should be evident when findings from a large number of studies, which have used several variants of these two tasks, are combined. If different neural systems are engaged by the two tasks, a formal statistical comparison of Go/NoGo and Stop-Signal findings should isolate these regions. The common and distinct aspects of inhibitory control that these two tasks tap into can then be evaluated in the context of existing knowledge of the neural systems identified.

Several meta-analyses of response inhibition tasks have been published (e.g., Buchsbaum et al., 2005; Nee et al., 2007; Simmonds et al., 2008; Swick et al., 2008). The initial meta-analysis by Buchsbaum et al. (2005) included 18 GNG papers and observed highly right-lateralized foci in the middle/inferior frontal gyri, inferior parietal/supramarginal gyri, and superior occipital gyrus. Nee et al. (2007) applied the density analysis technique to 47 studies of interference resolution that employed Stroop, flanker, GNG, stimulus–response compatibility, Simon, and SST tasks. A separate meta-analysis of the 14 GNG experiments (Go vs. NoGo contrast only) revealed a very prominent cluster in the right dorsolateral PFC extending into the IFG and insula, with smaller clusters in the left dorsolateral PFC, ACC, and right posterior parietal cortex. Simmonds et al. (2008) classified 11 event-related fMRI studies of GNG as either simple (the NoGo stimulus was always the same) or complex (the NoGo stimulus changed depending on context). Common to both task types was greater activation in the pre-SMA during NoGo vs. Go or a low-level baseline. Activation in the right dorsolateral PFC was observed only in the complex tasks, which taxed working memory to a greater extent. Thus, the specific pattern of additional frontal and posterior regions that are recruited may vary according to task demands.

However, none of these previous studies have looked at GNG and SST separately. To fill this gap, the present paper conducted a quantitative meta-analytic review of the neuroimaging literature to determine the common and unique patterns of brain activity obtained across the two response inhibition tasks. We wished to determine whether (and to what extent) the neuroanatomical correlates of task performance in GNG and SST can be dissociated. If they activate non-overlapping brain regions, one can assume that the two tasks engage different cognitive processes (Lenartowicz et al., 2010). We used the Activation Likelihood Estimation (ALE) method, a quantitative meta-analysis technique (Laird et al., 2005a) to infer function–location relationships from the functional neuroimaging literature. The present study is the largest and most inclusive meta-analysis of response inhibition to date, with 48 GNG papers and 21 SST papers, and is the first to present a separate analysis of the Stop-Signal task.

## Materials and methods

### *Searches and inclusion criteria*

To explore whether different subtypes of response inhibition can be dissociated neuroanatomically, we conducted separate quantitative meta-analyses of functional imaging data from GNG and SST using the ALE method (Laird et al., 2005a). To help identify appropriate papers, we used BrainMap, a searchable online database created and developed at the Research Imaging Center of the University of Texas Health Science Center San Antonio, and PubMed searches. The criteria for inclusion in the meta-analyses were as follows: (1) behavioral tasks were restricted to Go/NoGo and Stop-Signal inhibition tasks; (2) manual responses used as the response modality; (3) studies must have been conducted in young control subjects; (4) papers that compared a clinical population to controls must have reported separate results for controls and patients; and (5) whole-brain analysis and full reporting of Talairach or MNI coordinates were also required for inclusion.

The Sleuth program (downloaded from http://brainmap.org/) searches for papers entered into the BrainMap database based on specified queries, such as Citation, Subjects, Conditions, Experiments, and Location. We searched within Experiments for Talairach coordinates reported in studies of action inhibition. As of late May 2010, Sleuth identified 81 papers reporting activations in the behavioral domain of action inhibition, and 34 of these were included in the meta-analysis. The other 47 studies were excluded because they failed to meet one or more of the inclusion criteria listed above. In addition, 32 more eligible papers (not included in the BrainMap database) were found through PubMed searches conducted through May 2010, which included the following search terms: go/nogo; stop signal; response inhibition AND frontal; and response inhibition AND prefrontal. Thus, a grand total of 66 papers were included in the analyses.

### *ALE algorithm*

The ALE meta-analysis followed the procedures of Laird et al. (2005a), as implemented in the GingerALE 1.1 program. Briefly, 3D coordinates in stereotactic space are pooled across different studies. Each point, or focus, is modeled by a 3D Gaussian distribution, defined by the full-width half-maximum (FWHM). The probability of activity occurring at a given voxel is calculated. Then the probability estimate for the entire voxel volume is calculated; this is defined as the ALE statistic. Permutation testing determines the null distribution of the ALE statistic at each voxel. The output is a map of $p$ values for each voxel. This map is thresholded using the false discovery rate (FDR) algorithm. Finally, a cluster analysis is performed on the thresholded map. We selected parameters recommended by the program, as outlined below.

### *Within-condition meta-analysis*

For the GNG task, the comparisons included in the meta-analysis were Successful NoGo vs. Go and Successful NoGo vs. Baseline (Table 1). For the SST task, comparisons included Successful Stop vs. Go, Successful Stop vs. Baseline, and Successful Stop vs. Unsuccessful Stop (Table 1). In total, the BrainMap database and PubMed searches identified 48 relevant papers reporting activations in GNG response inhibition tasks: 830 foci in 68 experiments (38 foci were outside the analysis mask used by the ALE algorithm). There were 21 papers identified for SST, with 458 foci in 34 experiments (4 foci were outside the mask). In the Sleuth program, “experiments” refers to individual contrasts between conditions, so each paper could have multiple experiments. Because there were over twice as many GNG papers as SST papers, 21 randomly selected GNG papers were included in a subsidiary analysis, with 337 foci in 31 experiments (16 foci were outside the analysis mask).

In the majority of experiments (80%), NoGo trials were contrasted with Go trials. The other contrast consisted of NoGo versus fixation or a low-level baseline. On the other hand, only 59% of SST papers contrasted Stop trials with Go trials. The most appropriate comparison condition in the Stop-Signal task has been debated to a greater extent in the literature (e.g., see Boehler et al., 2010). Other reported contrasts have included Successful Stop vs. Unsuccessful Stop trials (Li et al., 2006b; Padmala and Pessoa, 2010), groups of subjects with a short vs. long stop signal RT (Li et al., 2006a,b), and hard vs. easy to inhibit trials (Matthews et al., 2005). Selective analysis of NoGo vs. Go trials only and Stop vs. Go trials only did not differ substantially from the original analyses that included all types of contrasts (e.g., Successful Stop vs. Unsuccessful Stop, subjects with a short vs. long SSRT, and hard vs. easy to inhibit trials), so only the latter are reported

**Table 1**
Studies included in the meta-analyses.

| First author | Year | B/E | n | Comparisons |
|---|---|---|---|---|
| *GNG only* | | | | |
| 1. Altshuler | 2005 | B | 4 | NoGo>Go, controls |
| 2. Asahi | 2004 | B | 11 | NoGo>Go |
| 3. Baglio | 2009 | E | 5 | NoGo vs. fixation, controls |
| 4. Bellgrove | 2004 | E | 19 | NoGo>Go |
| 5. Borgwardt | 2008 | E | 5 | NoGo>oddball, placebo |
| 6. Braver | 2001 | E | 11 | NoGo>Go, disjunction analysis |
| 7a. Chikazoe | 2009 | E | 52 | NoGo>Frequent–Go |
| 7b. Chikazoe | 2009 | E | 52 | NoGo>Infrequent–Go |
| 8a. Chuah | 2006 | E | 5 | NoGo vs. Go, rested wakefulness |
| 8b. Chuah | 2006 | B | 9 | Blocked task effects vs. fixation |
| 9a. de Zubicaray | 2000 | B | 15 | Increased activations for refrain vs. Go |
| 9b. de Zubicaray | 2000 | B | 11 | Linear increases w/ # trials equated per block |
| 10. Dillo | 2010 | B | 2 | 50/50 Go/NoGo vs. Go blocks |
| 11. Falconer | 2008 | E | 6 | NoGo/Go, controls |
| 12a. Fassbender | 2004 | B | 21 | Blocked task effects vs. rest |
| 12b. Fassbender | 2004 | E | 8 | NoGo>Go, correct |
| 13. Garavan | 1999 | E | 14 | Successful NoGo>Go |
| 14. Garavan | 2002 | E | 16 | Successful NoGo>Go |
| 15a. Garavan | 2003 | B | 12 | Blocked task effects vs. rest |
| 15b. Garavan | 2003 | E | 7 | NoGo>Go, event-related Stops |
| 16. Goghari | 2009 | E | 8 | NoGo>Go, probe-related activity |
| 17. Hester | 2004 | E | 21 | Successful NoGo>Go, cued and uncued |
| 18. Horn | 2003 | B | 13 | Go/NoGo>Go |
| 19. Kaladjian | 2007 | E | 11 | Correct NoGo vs. correct Go |
| 20a. Kaladjian | 2009a | E | 12 | NoGo vs. Go, healthy controls, T1 (session 1) |
| 20b. Kaladjian | 2009a | E | 8 | NoGo vs. Go, healthy controls, T2 (session 2) |
| 21. Kaladjian | 2009b | E | 16 | NoGo>Go, correct trials, healthy controls |
| 22. Karch | 2008 | E | 13 | NoGo>control condition, healthy controls |
| 23a. Kawashima | 1996 | B | 18 | Go/NoGo>Go and response selection tasks>rest |
| 23b. Kawashima | 1996 | B | 21 | Go/NoGo>rest |
| 24a. Kelly | 2004 | E | 23 | NoGo>Go, fast and slow |
| 24b. Kelly | 2004 | E | 7 | NoGo>Go, fast>slow |
| 25. Kiehl | 2000 | E | 8 | NoGo>Go, correct rejects |
| 26. Konishi | 1998 | E | 19 | NoGo>Go, No-Go dominant foci |
| 27. Konishi | 1999 | E | 1 | NoGo>Go, No-Go dominant foci |
| 28. Langenecker | 2007 | E | 8 | NoGo>Go, correct rejections, controls |
| 29a. Laurens | 2005 | E | 12 | NoGo>rest baseline, conjunction analysis, (auditory and visual) |
| 29b. Laurens | 2005 | E | 4 | NoGo>Go |
| 30a. Lawrence | 2009 | E | 1 | No-Go>Oddball |
| 30b. Lawrence | 2009 | E | 2 | No-Go>Go |
| 31a. Liddle | 2001 | E | 19 | Correct NoGo — baseline |
| 31b. Liddle | 2001 | E | 23 | Correct NoGo — Go |
| 32a. Maguire | 2003 | B | 10 | Go/NoGo vs. visual control fixation |
| 32b. Maguire | 2003 | B | 6 | Go/NoGo vs. Go |
| 33. Maltby | 2005 | E | 5 | NoGo>Go, correct rejections, controls |
| 34. Mazzola-Pomietto | 2009 | E | 7 | NoGo>Go, healthy controls |
| 35a. McNab | 2008 | E | 17 | NoGo>Oddball |
| 35b. McNab | 2008 | E | 6 | NoGo>Go |
| 35c. McNab | 2008 | E | 7 | Go/NoGo, Stop Tasks vs. Oddball, Conjunction |
| 35d. McNab | 2008 | E | 6 | Go/NoGo, Stop Tasks vs. Go, Conjunction |
| 36. Menon | 2001 | B | 13 | Go/NoGo vs. Go |
| 37. Mobbs | 2007 | B | 4 | Go/NoGo blocks vs. Go only |
| 38a. Mostofsky | 2003 | E | 3 | NoGo>fixation, simple |
| 38b. Mostofsky | 2003 | E | 3 | NoGo>fixation, counting |
| 39. Nakata | 2008 | E | 33 | Somatosensory movement NoGo vs. baseline |
| 40. Roth | 2007 | E | 13 | NoGo>Go, control subjects |
| 41a. Rubia | 2001 | B | 12 | Generic NoGo>Go |
| 41b. Rubia | 2001 | B | 9 | Activation common to all GNG and Stop Tasks |
| 42. Rubia | 2006 | E | 11 | NoGo>Go, adults |
| 43. van Gaal | 2010 | E | 29 | Weakly masked trials: No/Go>Go |
| 44a. Wager | 2005 | E | 13 | NoGo>Go |
| 44b. Wager | 2005 | E | 12 | NoGo>Go, unique regions |
| 45. Walther | 2010 | E | 31 | Conjunction analysis, auditory and visual, NoGo>Go |
| 46a. Watanabe | 2002 | E | 5 | NoGo>Go |
| 46b. Watanabe | 2002 | E | 4 | NoGo>Go, specific activation areas |
| 47. Welander-Vatn | 2009 | B | 12 | Go/NoGo>fixation, healthy controls |
| 48a. Zheng | 2008 | E | 8 | Successful NoGo — Go |
| 48b. Zheng | 2008 | E | 2 | Go/NoGo and Stop Signal, common areas |
| *SST only* | | | | |
| 1. Aron | 2006 | E | 35 | StopInhibit — Go (Stop trials w/o button press — Go) |
| 2. Aron | 2007 | E | 38 | Critical StopInhibit vs. critical Go |
| 3a. Boehler | 2010 | E | 3 | Successful Stop>unsuccessful Stop |
| 3b. Boehler | 2010 | E | 30 | Successful Stop>Go |

**Table 1** *(continued)*

| First author | Year | B/E | n | Comparisons |
|---|---|---|---|---|
| *SST only* | | | | |
| 3c. Boehler | 2010 | E | 23 | Successful Stop>Go; and unsuccessful Stop>Go |
| 3d. Boehler | 2010 | E | 13 | Successful Stop>control block Stop; and unsuccessful Stop>control block Stop |
| 4a. Chikazoe | 2009 | E | 57 | Stop vs. uncertain-Go |
| 4b. Chikazoe | 2009 | E | 16 | Disjunction analysis, Stop vs. uncertain-Go |
| 5a. Cai | 2009 | E | 8 | Color Task, successful Stop vs. Go |
| 5b. Cai | 2009 | E | 14 | Orientation Task, successful Stop vs. Go |
| 6. Chamberlain | 2009 | E | 33 | Successful Stop vs. Go |
| 7. Chevrier | 2007 | E | 3 | Successful Stop vs. Go |
| 8. Leung | 2007 | E | 7 | Conjunction analysis, eye and hand, Stop — Go |
| 9. Li | 2006a | E | 5 | Short>long SSRT |
| 10a. Li | 2006b | E | 9 | Successful>failed inhibitions |
| 10b. Li | 2006b | E | 3 | Short vs. long Stop-Signal processing time |
| 11. Matthews | 2005 | E | 6 | Hard vs. easy inhibit trials |
| 12a. McNab | 2008 | E | 17 | NoGo>Oddball |
| 12b. McNab | 2008 | E | 6 | NoGo>Go |
| 12c. McNab | 2008 | E | 7 | Conjunction: GNG and Stop Tasks (vs. Oddball) |
| 12d. McNab | 2008 | E | 6 | Conjunction: Go/NoGo and Stop Tasks (vs. Go) |
| 13. Padmala | 2010 | E | 14 | Successful>unsuccessful Stop trials |
| 14. Ramautar | 2006 | E | 7 | Successful Stop — Go (pooled across low- and high-frequency conditions) |
| 15a. Rubia | 2001 | B | 6 | SSRT blocks vs. Go only blocks, collapsed across probability conditions |
| 15b. Rubia | 2001 | B | 9 | Activation common to all GNG and SSRT versions |
| 16. Rubia | 2003 | E | 2 | Successful — unsuccessful Stop trials |
| 17a. Sharp | 2010 | E | 10 | Stop correct vs. Go |
| 17b. Sharp | 2010 | E | 6 | Stop correct vs. continue |
| 18. Stratkowski | 2008 | E | 14 | Correct Stop vs. correct Go |
| 19a. Vink | 2005 | B | 4 | Go/Stop>Go only |
| 19b. Vink | 2005 | B | 4 | Parametric analysis, Go/Stop>Go only |
| 20. Xue | 2008 | E | 13 | StopInhibit — Go trials, manual |
| 21a. Zheng | 2008 | E | 10 | Successful Stop — Go |
| 21b. Zheng | 2008 | E | 2 | Go/NoGo and Stop-signal, common areas |

List of studies including first author, year of publication, whether the design was blocked or event-related (B/E) and the number (n) of activation foci entered into the activation likelihood estimation (ALE) meta-analyses. There were 66 papers with a total of 48 Go No/Go and 21 SST. Three used both tasks (Rubia et al., 2001; McNab et al., 2008; Zheng et al., 2008.

in detail. In each case, the original (more inclusive) analysis had a slightly larger extent of activation, with one very small cluster for GNG and 3 small clusters for SST (see Supplementary Tables S1A and S1B).

Since activation foci in BrainMap are specified using Talairach coordinates, the GingerALE 1.1 program was used to make appropriate conversions from MNI to Talairach space using the icbm2tal transform (Lancaster et al., 2007) when required for papers identified through PubMed. A recent study demonstrated that the "Lancaster" transform was more accurate than the "Brett" transform in reducing the disparity between MNI and Talairach coordinates (Laird et al., 2010). Therefore, we followed the procedures recommended by Laird et al., which are implemented in GingerALE. Any papers that converted MNI to Talairach space using the mni2tal Brett transform (Brett et al., 2002) were converted back to MNI and reconverted using the icbm2tal Lancaster transform. Table 1 shows the list of studies that were included in the analysis and the number of activation foci for each (see Supplementary References for full citations). The Talairach coordinates of all inhibitory control-related activations were used to estimate voxel-wise activation likelihoods. A full-width half-maximum (FWHM) of 12 mm, permutation testing with 5000 iterations, a false discovery rate threshold of 0.01, and a cluster extent threshold of 100 $mm^3$ were applied to the data. Clusters were overlaid on the optimized Colin Brain (Kochunov et al., 2002), and the resulting maps identified the regions of activation common to successful response inhibition in the Go/NoGo task (Fig. 1A) and the Stop-Signal task (Fig. 1B).

### *Between-condition meta-analysis*

Similar to the study of Sörös et al. (2009), differences between the two within-condition ALE maps were obtained by subtraction using GingerALE (Laird et al., 2005a). To determine these differences, the ALE values for the SST analysis were subtracted from those for the GNG analysis at each voxel using the coordinates from Table 1. The resulting values were entered into a permutation test (5000 permutations) to determine the statistical differences between tasks. As for the within-condition meta-analyses, the FWHM was 12 mm, false discovery rate was 0.01, and the minimum cluster size was 100 $mm^3$. The resultant ALE map shows regions in which the two groups of foci are significantly different.

A conjunction analysis showed the common areas of overlap between the two tasks (Figs. 2 and 3). Using custom-made MATLAB scripts, voxels common to both the GNG and SST maps, as well as voxels unique to either one of the maps, were isolated. A scale was generated where the values of the ALE statistics run from 0 to 0.05 for those voxels that are found only in the GNG map (purple-blue), from 0.05 to 0.1 for the voxels that are in the SST map only (pink-red), and from 0.1 to 0.2 for the voxels common to both maps (orange-yellow). For the last portion of the scale, the sum of the GNG and SST ALE statistics were used.

## Results

The largest and most significant activation foci were observed in the anterior insula in both tasks (Fig. 1). Surprisingly, activations in SST were more bilaterally represented in the insular cortex than activations in GNG, which also showed a strong right lateralization in the middle frontal gyrus and inferior parietal cortex. Although one of the clusters extended into RIFG in the SST task, the maximal overlap across studies as estimated by the ALE algorithm was in the insula, not in the IFG. In addition, there was a separate LIFG cluster in the GNG task.

### *Go/NoGo*

For GNG (Table 2 and Fig. 1A), 12 separate clusters were identified. Major clusters were centered in the right insula (BA 13) and right middle frontal gyrus (BA 9), the right inferior parietal lobule/

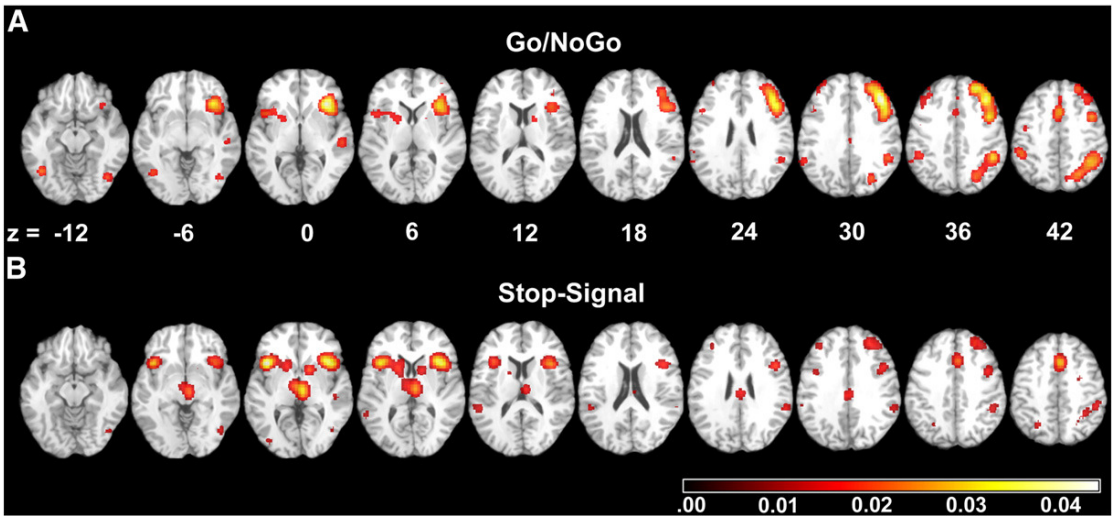


**Fig. 1.** Activation likelihood estimation (ALE) map showing significant inhibition-related activation clusters overlaid on the optimized Colin Brain (Kochunov et al., 2002). The left side of the brain is on the left side of the scan. (A) Studies using the Go/NoGo (GNG) task. (B) Studies using the Stop-Signal Task (SST). The z locations for both maps are illustrated under the slices in (A). The scale bar shows the ALE statistic, which becomes more significant from left (dark red) to right (white).

precuneus (BA 40, 19, 7), and the superior frontal gyrus (medial BA 6, 8). Also notable are large clusters in the left middle and inferior frontal gyri (BA 9, 6, 44) and the left insula/putamen/claustrum, which overlaps with the insular region damaged in the left IFG patients in our lesion study (Swick et al., 2008).

The secondary GNG analysis with 21 randomly selected papers (matching the number included in SST) revealed similar results. The largest clusters were in the right middle frontal gyrus (BA 9, 46, 6), the right insula, the right inferior parietal lobule, and the left putamen/claustrum (see Supplementary Table S2). A cluster in the superior/medial frontal gyri (BA 6) was still obtained in this subanalysis but it was smaller.

### *Stop-Signal*

For SST (Table 3 and Fig. 1B), 15 separate clusters were identified. The largest cluster was in the left insula extending into subcortical structures (thalamus and putamen) and the posterior cingulate (BA 23). Other major clusters were centered in the right insula extending into inferior and precentral gyri (BA 9), the superior frontal gyrus (medial BA 6), the right middle frontal gyrus (BA 9), and the right inferior parietal lobule (BA 40).

### *Comparison between conditions*

Activation foci common to the two tasks were depicted by overlaying the two ALE maps (Fig. 2). Maximal overlap was observed in the right insular cortex (Fig. 3A) and medial BA 6 (Fig. 3B). Differences between the conditions were obtained by subtraction, revealing a very large cluster focused in the right middle and superior frontal gyri (BA 9) (Table 4). Another large cluster was also located on the right in the inferior parietal lobule (BA 40) and precuneus (BA 7, 19). Both of these right-lateralized clusters were activated to a greater extent in GNG than SST. Only two foci, in the thalamus and the left insula, were more active in SST than in GNG (Fig. 4).

## Discussion

Quantitative meta-analysis of two widely used motor inhibition tasks produced overlapping as well as distinctive regions of activation. These comprehensive new ALE results clearly demonstrate the importance of bilateral anterior insular regions and medial BA 6 (SMA/pre-SMA) for successful performance in response inhibition tasks, as these were common areas activated across both GNG and SST. According to Dosenbach et al. (2006), these two regions comprise a “core system” that controls task set. Localization in that study was

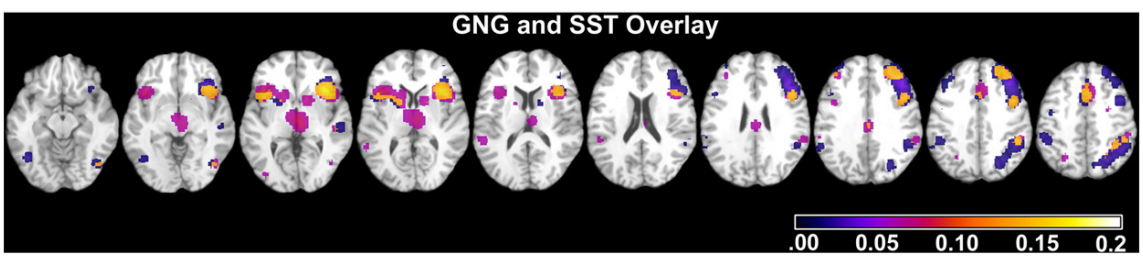


**Fig. 2.** ALE map showing an overlay of the significant clusters of activation obtained in each task. The conjunction analysis was generated using MATLAB scripts to isolate voxels common to both the GNG and SST maps, as well as voxels unique to either one of the maps. The scale bar (in arbitrary units) represents values of the ALE statistic from 0 to 0.05 for voxels found in the GNG map only (purple-blue), from 0.05 to 0.1 for voxels in SST only (pink-red), and from 0.1 to 0.2 for voxels common to both maps (orange-yellow). For the last portion of the scale, the sum of the GNG and SST ALE statistics was used.

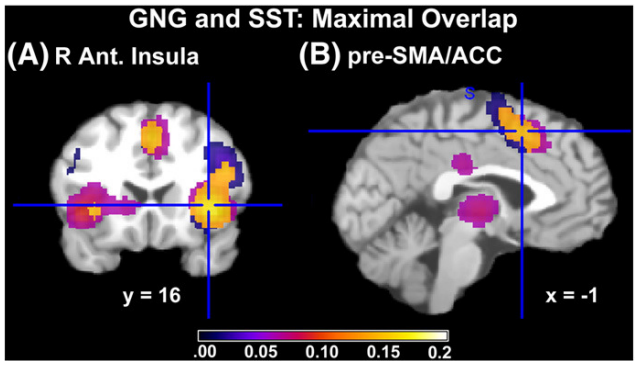


**Fig. 3.** Regions of maximal overlap in the two tasks are located in the cingulo-opercular control network. The scale bar (in arbitrary units) represents values of the ALE statistic from 0 to 0.05 (purple-blue) for voxels found in the GNG map only (purple-blue), from 0.05 to 0.1 for voxels in SST only (pink-red), and from 0.1 to 0.2 for voxels common to both maps (orange-yellow). (A) Coronal section through the anterior insula. Crosshairs are placed at MNI coordinates 36, 16, 4 (reported by Dosenbach et al., 2006 as one of the three major foci involved in the implementation of task set). (B) Sagittal section including the medial superior frontal gyrus and dorsal ACC. Crosshairs are placed at MNI coordinates −1, 10, 48 (reported by Dosenbach et al., 2006 as another one of the major foci of the core system that controls task set).

determined by combining results from ten tasks that used mixed blocked/event-related designs, then finding the conjunction of activity related to start cues, sustained set-maintenance, and performance errors (Dosenbach et al., 2006). The peak coordinates of this core system are remarkably close to the maximal overlap of the GNG and SST meta-analyses shown in Fig. 3. Other investigators have characterized these brain regions more broadly, as part of a "salience network" activated by personally relevant stimuli that can be cognitive, emotional, visceral, or autonomic in nature (Seeley et al., 2007).

**Table 2**
GNG clusters.

| | Cluster brain region | BA | x | y | z | Vol ($mm^3$) | Extrema value |
|---|---|---|---|---|---|---|---|
| 1 | R insula | 13 | 34 | 22 | 0 | 30,808 | 0.0396 |
| | R middle frontal gyrus | 9 | 40 | 28 | 32 | | 0.0327 |
| | R middle frontal gyrus | 9 | 26 | 42 | 36 | | 0.0311 |
| | R inferior frontal gyrus | 9 | 46 | 12 | 30 | | 0.0276 |
| 2 | R inferior parietal lobule | 40 | 48 | −44 | 36 | 8704 | 0.0250 |
| | R inferior parietal lobule | 40 | 40 | −50 | 44 | | 0.0247 |
| 3 | R medial frontal gyrus | 6 | 0 | 12 | 46 | 5200 | 0.0186 |
| | R medial frontal gyrus | 6 | 2 | 2 | 58 | | 0.0184 |
| 4 | L claustrum | – | −30 | 14 | 0 | 2240 | 0.0166 |
| | L putamen | – | −18 | 4 | 4 | | 0.0155 |
| 5 | L inferior parietal lobule | 40 | −46 | −40 | 40 | 2048 | 0.0228 |
| 6 | L middle frontal gyrus | 9 | −34 | 32 | 34 | 2008 | 0.0141 |
| | L superior frontal gyrus | 9 | −40 | 38 | 28 | | 0.0140 |
| | L superior frontal gyrus | 9 | −32 | 48 | 26 | | 0.0138 |
| | L middle frontal gyrus | 9 | −40 | 28 | 36 | | 0.0138 |
| 7 | R precuneus | 19 | 28 | −70 | 32 | 1544 | 0.0170 |
| 8 | R superior temp gyrus | 21 | 52 | −26 | −2 | 1480 | 0.0186 |
| 9 | L supramarginal gyrus | 40 | −56 | −50 | 28 | 1384 | 0.0170 |
| | L inferior parietal lobule | 40 | −58 | −38 | 26 | | 0.0139 |
| 10 | R inferior occip gyrus | 19 | 42 | −70 | −8 | 992 | 0.0177 |
| 11 | L fusiform gyrus | 37 | −40 | −60 | −12 | 928 | 0.0186 |
| 12 | L inferior frontal gyrus | 44 | −48 | 12 | 22 | 784 | 0.0152 |
| 13 | R middle frontal gyrus | 10 | 34 | 50 | 4 | 416 | 0.0141 |
| 14 | R caudate body | – | 14 | 4 | 10 | 304 | 0.0148 |
| 15 | R cingulate gyrus | 23 | 2 | −24 | 30 | 176 | 0.0136 |
| 16 | L inferior parietal lobule | 40 | −42 | −50 | 52 | 120 | 0.0117 |

Significant cluster locations from the GNG meta-analysis, thresholded at $p<0.01$ (FDR-corrected for multiple comparisons), along with Brodmann area (BA), Talairach coordinates (x, y, z) of the peak voxel, cluster volume ($mm^3$), and extrema value (maximum ALE score). Larger scores indicate a greater likelihood of activation for a given cluster. L = left, R = right.

**Table 3**
SST clusters.

| | Cluster brain region | BA | x | y | z | Vol ($mm^3$) | Extrema value |
|---|---|---|---|---|---|---|---|
| 1 | L insula | – | −40 | 14 | 0 | 21,648 | 0.0427 |
| | R thalamus | – | 6 | −20 | 0 | | 0.0311 |
| | L putamen | – | −16 | 10 | 4 | | 0.0193 |
| | R cingulate gyrus | 23 | 2 | −24 | 28 | | 0.0177 |
| 2 | R insula | – | 38 | 16 | 2 | 13,776 | 0.0386 |
| | R inferior frontal gyrus | 9 | 44 | 12 | 22 | | 0.0190 |
| | R precentral gyrus | 9 | 42 | 4 | 34 | | 0.0170 |
| 3 | R medial frontal gyrus | 6 | 4 | 14 | 44 | 10,640 | 0.0292 |
| 4 | R middle frontal gyrus | 9 | 26 | 40 | 34 | 3472 | 0.0193 |
| 5 | R inferior parietal lobule | 40 | 58 | −40 | 26 | 3088 | 0.0161 |
| | R inferior parietal lobule | 40 | 48 | −40 | 40 | | 0.0152 |
| | R inferior parietal lobule | 40 | 34 | −48 | 42 | | 0.0139 |
| 6 | R lentiform, Lat GP | – | 14 | 6 | 0 | 1944 | 0.0204 |
| 7 | L superior temporal gyrus | 13 | −50 | −40 | 16 | 1192 | 0.0142 |
| | L middle temporal gyrus | 22 | −56 | −50 | 6 | | 0.0115 |
| 8 | R inferior occipital gyrus | 19 | 44 | −70 | −8 | 808 | 0.0142 |
| 9 | L superior frontal gyrus | 9 | −34 | 36 | 28 | 704 | 0.0141 |
| 10 | R middle frontal gyrus | 6 | 28 | −4 | 46 | 600 | 0.0137 |
| | R middle frontal gyrus | 6 | 30 | 0 | 54 | | 0.0122 |
| 11 | L superior parietal lobule | 7 | −24 | −62 | 42 | 528 | 0.0139 |
| 12 | L precentral gyrus | 9 | −40 | 4 | 32 | 344 | 0.0132 |
| 13 | L middle occipital gyrus | 18 | −36 | −84 | 0 | 208 | 0.0121 |
| 14 | R superior temporal gyrus | 22 | 46 | −26 | 0 | 152 | 0.0120 |
| 15 | R superior parietal lobule | 7 | 26 | −56 | 46 | 144 | 0.0116 |

Significant cluster locations from the SST meta-analysis, thresholded at $p<0.01$ (FDR-corrected for multiple comparisons), along with Brodmann area (BA), Talairach coordinates (x, y, z) of the peak voxel, cluster volume ($mm^3$), and extrema value (maximum ALE score). Larger scores indicate a greater likelihood of activation for a given cluster. L = left, R = right, GP = globus pallidus.

### *Core response inhibition system*

Although not emphasized in most previous studies of response inhibition and interference resolution, Wager, Nee, and colleagues have noted the importance of the bilateral anterior insular cortex for these functions (Wager et al., 2005; Nee et al., 2007). The prominence

**Table 4**
GNG–SST clusters.

| | Cluster brain region | BA | x | y | z | Vol ($mm^3$) | Extrema value |
|---|---|---|---|---|---|---|---|
| 1 | R middle frontal gyrus | 9 | 40 | 26 | 30 | 13,032 | 0.0391 |
| | R superior frontal gyrus | 8 | 24 | 42 | 38 | | 0.0190 |
| | R precentral gyrus | 9 | 40 | 6 | 40 | | 0.0172 |
| 2 | R inferior parietal lobule | 40 | 42 | −54 | 44 | 6768 | 0.0238 |
| | R precuneus | 7 | 24 | −70 | 42 | | 0.0188 |
| | R inferior parietal lobule | 40 | 48 | −46 | 36 | | 0.0177 |
| | R precuneus | 19 | 30 | −72 | 30 | | 0.0171 |
| 3 | R thalamus | – | 4 | −16 | 0 | 3952 | −0.0245 |
| 4 | L insula | 13 | −40 | 16 | 0 | 1536 | −0.0278 |
| 5 | R inferior frontal gyrus | 47 | 36 | 26 | −2 | 1472 | 0.0220 |
| 6 | L precentral gyrus | 4 | −42 | −14 | 48 | 1064 | 0.0164 |
| 7 | L fusiform gyrus | 37 | −40 | −62 | −12 | 1056 | 0.0205 |
| 8 | L supramarginal gyrus | 40 | −56 | −50 | 30 | 744 | 0.0165 |
| 9 | R middle frontal gyrus | 10 | 36 | 48 | 4 | 480 | 0.0153 |
| 10 | L inferior parietal lobule | 40 | −44 | −40 | 40 | 480 | 0.0178 |
| 11 | L inferior frontal gyrus | 44 | −50 | 12 | 20 | 296 | 0.0149 |
| 12 | L superior frontal gyrus | 9 | −30 | 48 | 30 | 216 | 0.0130 |

Significant cluster locations showing the differences between the two tasks, obtained from the subtraction meta-analysis, thresholded at $p<0.01$ (FDR-corrected for multiple comparisons), along with Brodmann area (BA), Talairach coordinates (x, y, z) of the peak voxel, cluster volume ($mm^3$), and extrema value (maximum ALE score). Larger scores indicate a greater difference between tasks for a given cluster. Positive extrema values, GNG>SST; negative extrema values, SST>GNG. L = left, R = right.

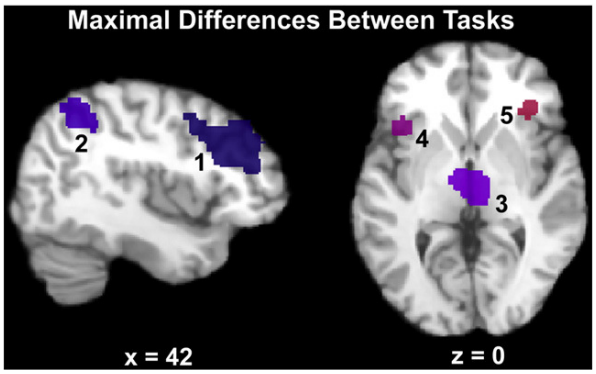


**Fig. 4.** Regions of maximal differences between tasks, obtained by the GNG–SST subtraction. GNG shows greater activation than SST in the fronto-parietal network: cluster 1 (R MFG) and cluster 2 (R IPL), as well as in RIFG (BA 47, cluster 5). SST shows greater activation than GNG in the cingulo-opercular network: cluster 3 (thalamus) and cluster 4 (L anterior insula). Cluster numbers correspond to those illustrated in Table 4 (each one shown in a different color).

of the left insula cluster in the present SST analysis was initially unexpected, based on the existing literature and its focus on RIFG. However, in a recent experiment using conjunction analyses (Successful and Unsuccessful Stop trials against a reference condition), the left anterior insula was the only brain region that showed a significant correlation with stopping efficiency (Boehler et al., 2010). Greater activation in the left anterior insula was associated with shorter Stop-Signal RTs (i.e., more efficient stopping).

In the broader context of task control processes, the anterior insula has been identified, using resting state functional connectivity MRI data, as one node in a large-scale control network that may be responsible for the maintenance of task set across trials (Dosenbach et al., 2007). This cingulo-opercular system, which includes the dorsal anterior cingulate/medial superior frontal cortex, the anterior insula/frontal operculum and the anterior PFC, shows sustained activity for the duration of a task epoch (Dosenbach et al., 2006). Given its ubiquity as an activated region in functional neuroimaging studies (see meta-analysis by Kurth et al., 2010), new views of the insula are emerging. Besides its well-established role in interoceptive awareness (Craig, 2009), major hypothesized functions include responding to salient events and initiating cognitive control (Menon and Uddin, 2010), maintaining task set and capturing focal attention (Nelson et al., 2010), and coordinating appropriate responses to internal and external events (Medford and Critchley, 2010). One possible implication for the present findings is that the insula may not play a specific role in response inhibition *per se*, but could instead maintain task rules and readiness. Boehler et al. (2010) made a similar argument: since an activity in the left anterior insula was associated with both stopping efficiency and overall accuracy in their Stop-Signal task, this region might support a more general cognitive control function.

Another common area of activation across tasks is the pre-SMA, the importance of which has been highlighted previously (Chao et al., 2009; Duann et al., 2009; Mostofsky and Simmonds, 2008). For example, participants with shorter Stop-Signal reaction times (and hence better inhibitory control abilities) showed greater activity in the pre-SMA, but not in the RIFG (Chao et al., 2009). These authors view the pre-SMA as a critical part of the circuit that implements response inhibition, along with basal ganglia regions. Other recent findings suggest that the pre-SMA is specifically associated with response inhibition, while RIFG activations are involved in attentional capture (Sharp et al., 2010) and attentional control (Hampshire et al., 2010). Both of those studies controlled for Stop-Signal attentional effects by including well-matched stimulus conditions (i.e., indicating a "continue" signal or a cue to respond to the previous stimulus, respectively) that did not require stopping. As a new theoretical framework incorporating these findings develops, the emerging emphasis is likely to be on well-circumscribed but anatomically distributed inhibitory control networks. A core element in these networks includes pre-SMA circuits, with recruitment of additional frontal and parietal regions based on task requirements (Mostofsky and Simmonds, 2008).

The bulk of the existing literature has emphasized the involvement of other regions in response inhibition. Namely, many neuroimaging studies have implicated right hemisphere regions in dorsolateral PFC (Zheng et al., 2008) and IFG (Aron and Poldrack, 2006) as being dominant for inhibitory control in these tasks. For the present GNG meta-analysis, prominent right lateralized clusters were, in fact, located in the middle frontal gyrus (MFG), as well as in the inferior parietal lobe (IPL). A notable cluster was also observed in the right insula, but the smaller left insular cluster was also significant. In contrast, the SST meta-analysis revealed that the insular clusters were strongly bilateral.

The RIFG has been viewed as the most critical region for stopping in prior studies (reviewed in Aron et al., 2004). Thus, an unexpected finding from the meta-analyses was the lack of a strong RIFG focus and the greater prominence of anterior insula foci in both tasks. There are two possible explanations for this observation. First, activation foci that include the insula might sometimes be interpreted as IFG activations. Although a common result in neuroimaging studies in general, the importance of the anterior insula in response inhibition tasks has not been widely discussed in the literature (but see Wager et al., 2005; Nee et al., 2007). However, its role is becoming increasingly recognized. Sharp et al. (2010) referred to the activated region in their study as the right IFG/insula, thereby acknowledging the locus/extent of activation in the insula. Second, the spatial smoothing methods used to analyze fMRI data can blur functionally distinct regions and cause activations to be mislocalized (Geissler et al., 2005; White et al., 2001). Spurious activations can also be observed at the group-level analysis based on highly smoothed data (Fransson et al., 2002). IFG activations that might be smoothed into the insula are perhaps aligned across spatially normalized single subject activation maps, so that at the group level the activation foci become likely to appear in the insula. Our findings therefore motivate a closer look at the relation between IFG and insula activations.

### *Attentional control systems*

When seen as pure response inhibition tasks, GNG and SST might have sustained attention components that are overlooked. In fact, Robertson and colleagues (Dockree et al., 2004; Robertson et al., 1997) have conceived of GNG as a "Sustained Attention to Response Task" (SART) when the probability of NoGo trials is low. Lapses of attention, as well as inhibitory deficits, can lead to false alarm errors. Attentional and strategic components in SST performance have been noted as well. The anticipation of a stop signal results in a chronic braking process, which is manifest as slower RTs in blocks where the stop signal is present, compared to when it is absent. Thus, subjects can adopt strategies that differentially emphasize speed vs. accuracy in task performance (Leotti and Wager, 2010). In addition, some versions of SST involve switching attention across modalities, from a visual target to an auditory Stop-Signal. Therefore, alternative interpretations of SST results are possible, incorporating both response inhibition processes and the ability to switch attention to the stop-signal tone (Bekker et al., 2005).

The GNG and SST tasks have often been used as interchangeable measures of response inhibition (Aron et al., 2004), but there are some differences between their neural substrates. In addition to the common areas in anterior insula and medial frontal cortex, there were

also distinct areas of activation in the two tasks (Table 4). For example, the large right hemisphere foci in MFG and IPL observed in GNG were significantly less prominent in SST. This was not an issue of reduced power in the SST analysis — it was replicated in an analysis with matched numbers of GNG experiments (see Supplementary Table S2). Conversely, a large thalamic focus was seen in SST but not GNG.

Could the two tasks reflect different aspects of response inhibition? Consistent with this notion, Eagle et al. (2008) divided action inhibition into different subtypes with distinct neuroanatomical and psychopharmacological correlates. This model of response inhibition considers the GNG task to be an example of action restraint, whereas SST is an example of action cancelation. Neuropsychological studies might be informative in this regard. Although performance on the two tasks was dissociated in children with ADHD, control children showed a correlation between restraint and cancelation tasks, suggesting shared resources (Schachar et al., 2007). This is in agreement with other findings that make this dichotomy of inhibitory processes less clear-cut (Zhang et al., 2008).

Verbruggen and Logan (2008a) have emphasized the differences between the tasks along another dimension, based on differential recruitment of automatic vs. controlled response inhibition processes. They argue that GNG typically uses consistent mappings for Go and NoGo stimuli that can be learned and automated through practice. In contrast, SST uses inconsistent mappings where Go stimuli can be Stop stimuli as well. Therefore, stopping must be accomplished through controlled means. The key point of our present findings, regardless of functional interpretation, is that GNG and SST activations are different. While the functional significance of this difference is an important empirical question (which is discussed below), it is clear that these two tasks are not equivalent, and caution is required when generalizing GNG or SST findings.

The thalamic and left insular clusters were both activated to a greater extent in the SST analysis than in GNG. Interestingly, the thalamus is part of the cingulo-opercular network. Might this suggest that SST places greater demands on task set implementation processes than GNG? Although the majority of studies included in the SST meta-analysis used event-related designs (thereby avoiding sustained task effects), portions of the cingulo-opercular network appear to be multifunctional and hypothesized to participate in phasic decision making and performance monitoring processes, as well as tonic task set maintenance (Dosenbach et al., 2008). Braver and Barch (2006) questioned this specific concept of the "task control network" and noted that alternative interpretations are possible, namely that the observed pattern of brain activity could reflect arousal rather than cognitive control. This proposal is a better fit with the broader conception of the "salience monitoring network" (Seeley et al., 2007).

The second task-control network identified from resting state data is the fronto-parietal system, which includes the dorsolateral prefrontal cortex and the intraparietal sulcus (Dosenbach et al., 2007). In contrast to the cingulo-opercular network, the fronto-parietal network is thought to mediate adaptive online control on a trial-to-trial basis. It appears to be highly similar to the dorsal attention system of Corbetta and Shulman (2002) and the executive control system of Seeley et al. (2007). In all of these conceptions, a key function is top-down adaptive control. This network, which was highly right lateralized in the present results, was more strongly active in the GNG meta-analysis than in SST. While the implications of Dosenbach et al.'s dual cognitive control networks model are still debated (e.g., Braver and Barch, 2006), we consider it significant that SST and GNG tasks seem to place differential demands on the cingulo-opercular and fronto-parietal networks, respectively. This is consistent with the position that these two response inhibition tasks are not engaging identical neural systems. Whether two distinct networks contribute to performance in tasks that require inhibitory control over response production, and whether the contribution of one or the other network is more pronounced depending on the nature of the task, is an important research question.

Thus, response inhibition is not a unitary process mediated by a distinct brain region. Instead, dissociable neural systems contribute to different components of inhibitory control over actions, which in turn are differentially engaged by the Go/NoGo and Stop-Signal tasks. Furthermore, some neural activations may not even be specific to response inhibition, instead reflecting attentional control and the detection of task-relevant cues more generally (Hampshire et al., 2010). Since inhibitory control is one of the core components of executive function, it will be critical to examine the constituent elements of these tasks and their underlying neural substrates more closely. One fruitful way of addressing these questions will be to conduct a series of within-subject experiments, using mixed blocked/event-related designs, to directly compare tonic and phasic activations in GNG and SST.

### *Broader implications*

The present results can inform future studies involving healthy subjects as well as various patient populations. Emerging efforts to develop a formal knowledge base of cognitive functions, such as the Cognitive Atlas and the Phenowiki (Bilder et al., 2009), operate under the assumption that defined constructs such as response inhibition can be reliably measured by specific tasks. If those tasks show demonstrably different patterns of neural activation, then they are not measuring the identical cognitive construct. Thus, our GNG and SST meta-analysis findings suggest that the current definition of response inhibition is in need of revision, in terms of delineating how it is measured (and *what* is measured).

A more formalized knowledge base, or cognitive ontology, is essential for genetic studies of psychiatric and neurodevelopmental disorders, because performance on a cognitive test of interest can be used for phenotyping purposes (Bilder et al., 2009). In fact, classification at the level of a cognitive test indicator has been emphasized as the foundation of cognitive ontologies. Behavioral genetics research has embraced the notion of endophenotypes — heritable biological or cognitive markers — that represent an intermediate phenotype between genes and a disease state. For example, a cohort study of 8 year old monozygotic and dizygotic twin pairs examined the heritability of response inhibition using a hybrid SST/GNG task (Schachar et al., 2010). A significant amount of variance in both measures of response inhibition could be accounted for by genetic factors, albeit with different percentages: the heritability of cancelation (as measured by SSRT) was found to be 50%, while the heritability of restraint (measured by accuracy on NoGo trials) was 27%. The hybrid task combined both GNG and SST trial types in one block, amplifying the similarity between the two tasks.

Thus, choice of task will play an important role in future studies in the field of "neuropsychiatric phenomics" (Bilder et al., 2009). In addition to genotyping, a logical next step in this general research program is to link the cognitive indicators to brain function using neuroimaging measures (Schachar et al., 2010). More precise knowledge of the common neural substrates that mediate response inhibition across tasks, compared to differential contributions from attention, retrieval of task rules, strategy implementation and performance adjustment, will help advance large-scale studies of patient populations, such as those with ADHD, obsessive–compulsive disorder, and bipolar disorder. Better understanding of the neural basis of inhibitory control will be possible by careful task analysis and integration of all the available patient and imaging data into a coherent framework.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.02.070.

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# Effects of working memory load on visual selective attention: behavioral and electrophysiological evidence

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Working memory and attention interact in a way that enables us to focus on relevant items and maintain current goals. The influence of working memory on attention has been noted in several studies using dual task designs. Multitasking increases the demands on working memory and reduces the amount of resources available for cognitive control functions such as resolving stimulus conflict. However, few studies have investigated the temporal activation of the cortex while multitasking. The present study addresses the extent to which working memory load influences early (P1) and late (P300) attention-sensitive event-related potential components using a dual task paradigm. Participants performed an arrow flanker task alone (single task condition) or concurrently with a Sternberg memory task (dual task condition). In the flanker task, participants responded to the direction of a central arrow surrounded by congruent or incongruent arrows. In the dual task condition, participants were presented with a Sternberg task that consisted of either four or seven consonants to remember prior to a short block of flanker trials. Participants were slower and less accurate on incongruent versus congruent trials. Furthermore, accuracy on incongruent trials was reduced in both dual task conditions. Likewise, P300 amplitude to incongruent flanker stimuli decreased when working memory load increased. These findings suggest that interference from incongruent flankers was more difficult to suppress when working memory was taxed. In addition, P1 amplitude was diminished on all flanker trials in the dual task condition. This result indicates that top-down attentional control over early visual processing is diminished by increasing demands on working memory. Both the behavioral and electrophysiological results suggest that working memory is critical in maintaining attentional focus and resolving conflict.

**Keywords: dual task, working memory, ERPs, attention, P1, P300**

## INTRODUCTION

Imagine driving along a busy suburban street with the radio blaring. While stopped at a light, the DJ on the radio announces that the 100th caller will win free tickets to a show you have wanted to see and then gives the phone number to call. As the light turns green, you rehearse the number in your head and drive through a complicated intersection with confusing signs. You take a wrong turn and end up on the freeway instead of the parking lot, where you had intended to stop and call the radio show number. Because you were focused on rehearsing the phone number and not attending to street signs, you were unable to call the radio for the tickets.

This scenario illustrates the difficulties of multitasking in everyday life. More specifically, attention was diminished when working memory capacity was loaded. Attention is regulated by a dynamic network that responds to both external events and internal goals (Yantis, 2000). Attention may be focused on specific visual features and objects driven by salient external events in an automatic fashion (bottom-up), or by internal expectations requiring cognitive control (top-down). Top-down attention influences the selection of visual stimuli based on previous experience and current goals, while filtering out distractor stimuli (Hopf and Mangun, 2000; Corbetta and Shulman, 2002; Bledowski et al., 2004; Lavie et al., 2004). Working memory plays a critical role in guiding these top-down attentional processes by keeping current goals in mind (Downing, 2000; de Fockert et al., 2001; Soto et al., 2005). But what happens when working memory is filled with items that are irrelevant for the goals required by a secondary task? In the example above, working memory was loaded with a seven-digit phone number and diminished the driver's capacity to attend to road-signs. Performance in this dual task scenario requires the coordination of multiple cognitive processes, including working memory, selective attention, and conflict resolution.

Lavie and colleagues (de Fockert and Lavie, 2001; Lavie et al., 2004; Lavie, 2005; Lavie and de Fockert, 2005) have demonstrated that increasing the demands on working memory reduces the ability to ignore irrelevant stimuli. They used a dual task design to manipulate the amount of information stored in working memory (one or six digits) while participants performed a flanker interference task (Lavie et al., 2004). In the letter flanker task, reaction times (RT) increased significantly when the flanker was incompatible with the target. This flanker interference effect was greater when working memory load was high relative to when it was low (de Fockert et al., 2001; Lavie et al., 2004; Lavie, 2005). This result shows that working memory is essential for overcoming response conflict and for optimal selective attention performance.

Few studies, however, have examined the effects of working memory load on neural activity in attention-sensitive visual regions during dual task performance. In one functional magnetic resonance imaging (fMRI) study, participants were presented with

a memory set followed by names of famous individuals superimposed over either compatible or incompatible faces (de Fockert et al., 2001). Activity in prefrontal cortex (PFC) was greater in the high working memory load condition than the low load condition. Furthermore, activity in the fusiform gyrus and extrastriate visual cortex was greater when distractor faces were present in the high load condition, relative to the low load condition. Thus, a high working memory load increased neural processing of distractors and resulted in greater behavioral interference.

Although fMRI identifies specific regions in the brain that are active in cognitive processing, it provides poor temporal resolution. Therefore, it is unclear whether activation reflects early or late changes in attention. The timing of cortical responses is a critical aspect of cognitive control and attention systems. Event-related potentials (ERPs) provide precise information regarding the timing of neural activity (Hillyard and Anllo-Vento, 1998). The present study adapted the design from Lavie et al. (2004) and examined the time-course of neuronal processing using ERPs during an attention task embedded within the delay period of a standard item recognition task. The number of items to be remembered was manipulated, and a single task condition without the memory load was also included. The neuronal time-course of changes in attention following working memory load was examined by investigating two specific ERP components: the P1 and the P300.

The P1 is an early visual component which peaks at approximately 80–120 ms over occipital regions. Dipole modeling and combined fMRI/ERP studies have suggested that the P1 is generated in extrastriate cortex (Di Russo et al., 2001). P1 is larger to stimuli that appear at an attended location compared to stimuli that appear at an unattended location (Hillyard and Anllo-Vento, 1998; Hillyard et al., 1998). In addition, researchers have noted that the P1 amplitude is *smaller* when perceptual load demands increase. For instance, increasing the number of irrelevant stimuli within a display caused a diminished P1 over the parietal–occipital region (Handy et al., 2001). Handy et al. (2001) concluded that an increase in perceptual load reduces the capacity to attend to specific attributes within the visual field. In addition, other researchers found that previously encoded spatial locations increase the attention-based component P1 (Awh et al., 2000). The authors concluded that spatial attention changes early visual processing by sustaining activation of locations in working memory (Awh et al., 2000). In contrast to these experiments on increasing perceptual load and the underlying effects on early selective attention, little is known about the effects of *cognitive* load on P1 amplitude.

Finding a decrease in P1 amplitude under conditions of cognitive load, such as working memory maintenance, would suggest that less attention was allocated for target detection in the secondary task. However, most studies have not employed dual task paradigms. The focus of prior research has been on the encoding, maintenance, or retrieval phases of working memory tasks. Task difficulty is manipulated by increasing the number or category of items that must be remembered. These studies have suggested that the P1 (and other early components) can be influenced by attention-driven, top-down modulation of visual processing (Gazzaley et al., 2008). However, to the best of our knowledge, no studies have investigated the effects of working memory load on the P1 elicited during a secondary, unrelated executive control task.

Another common ERP component related to attention is the P300, a positive wave from approximately 300–650 ms that is maximal over the central–parietal region. The P300 is associated with shifts in attention that update representations in working memory (Polich and Kok, 1995). P300 amplitude decreases when attention is directed away from the current target (Duncan et al., 2009). The P300 is also sensitive to demands placed on working memory (Wintink et al., 2001). Wintink et al. (2001) found that the P300 decreased by one microvolt over the parietal region for each additional item placed in working memory in an n-back task. In another n-back task, researchers found that the P300 also decreased when more items were maintained in working memory (Watter et al., 2001). These authors argued that the n-back task is a type of dual task paradigm requiring participants to update working memory as well as match current stimuli to encoded items in working memory. Therefore, the P300 may be an index of attention processing and working memory demands.

The goal of the current experiment is to examine the importance of working memory and cognitive control processes for the resolution of response conflict in a demanding visual attention task. Just like the scenario in the beginning, it did not matter whether the phone number rehearsed was accurately remembered. Rehearsing the phone number diminished visual attention to nearby road-signs, and the caller was never able to enter the contest. To investigate the extent to which working memory load decreases attention, we extended previous research (Lavie et al., 2004) by employing a *verbal* working memory task and examining the subsequent effects on conflict resolution in a *visual* selective attention task. Specifically, we investigated the effects of cognitive load on selective attention using concurrent Sternberg memory and flanker interference tasks. Both behavioral and ERP responses were used to detect changes in attentional control due to varying demands on working memory. We used a modified version of the Eriksen flanker task (Eriksen and Eriksen, 1974) to examine selective attention and cognitive control processes. Irrelevant flanker stimuli could be either congruent or incongruent with the central target. Participants performed the flanker task alone and in conjunction with a working memory task. Similar to the studies reported by Lavie et al. (2004, 2005), we varied cognitive load by using a memory set containing either four or seven items. These items then had to be maintained over the delay period during which a flanker task was performed. Based on previous behavioral findings, it was expected that incongruent flankers would increase RTs, specifically in the high working memory load condition (Lavie et al., 2004, 2005).

We also predicted that high working memory load would affect attentional ERP responses over the occipital and parietal regions. Similar to Wintink et al. (2001), we expected to find a decrease in P300 amplitude over the parietal region when cognitive load was increased. In addition, we expected that working memory demands would tax PFC regions that send top-down cortical projections to the visual cortex, thereby influencing early attentional processing (de Fockert et al., 2001; Krawczyk et al., 2007). Therefore, we expected to find significant changes in P1 amplitude, indicating that early attentional processing in the visual cortex is diminished in the high working memory load condition. Specifically, if items are being maintained in working memory, then fewer neural resources in PFC will be available for the flanker task, thereby resulting in decreased ability to resolve response conflict (Lavie and De Fockert,

2005). No study has investigated such effects on both the P1 and P300 attention components using a dual task design that manipulates cognitive load, so the current results will provide novel insights into the temporal parameters of top-down attentional control.

## MATERIALS AND METHODS

### PARTICIPANTS

Sixteen healthy, young participants (aged 18–30, 8 female) completed the dual task experiment, none of whom reported a history of neurological or psychological disorder, or significant substance abuse. Due to excessive noise, 1 subject was excluded from the analysis; the data from the remaining 15 are reported here. The experimental protocol was approved by the Institutional Review Board of VA Northern California Health Care System, and all participants gave informed consent prior to beginning the experiment. They were paid for transportation expenses plus $20/h for their participation.

### PROCEDURE

Participants were tested in a darkened, sound-attenuated room. EEG was recorded from 48 electrode sites positioned according to the 10/20 system (Jasper, 1958). All participants were instructed to fixate at the center of the screen and to blink as little as possible. Each participant completed both single and dual task flanker conditions as well as a single task Sternberg condition. The order was counterbalanced across participants. In both the single and dual task conditions, flanker stimuli were presented for 200 ms. Inter-trial interval varied randomly between 600 and 800 ms after the participant's response. If no response was made, the trial terminated after 900 ms. All tasks were divided into 10 blocks of trials, each block lasting about 3 min. The total test time required was approximately 2 h.

### STIMULI AND TASKS

#### *Single task condition, flanker*

Participants responded with a button press to indicate whether the central arrowhead pointed to the left or the right. Flanking arrows, positioned either above, below, or both above and below the central arrow, could point in either the same (congruent) or different (incongruent) direction (see **Figure 1**). Forty percent of trials had congruent flankers; 60% of trials had incongruent flankers. The asymmetrical and symmetrical flankers were equally presented in the congruent and incongruent conditions. Participants were instructed to respond as quickly and accurately as possible to the central arrow. Each participant completed 10 blocks of 60 flanker trials.

#### *Sternberg condition*

Participants were instructed to remember either four or seven consonants. In the set size 4 condition, the stimuli were presented for 2000 ms, whereas the set size 7 condition was presented for 3500 (i.e., a 500-ms encoding time for each letter in the memory set). After an 8.5-s delay, another consonant was presented. Participants responded with a button press to indicate whether or not this item was from the memory set. Half of the trials had probes that were from the memory set and half were not. Each block contained 10 Sternberg trials randomly selected to present half the trials with four items and the other half with seven items. There were a total of 10 blocks.

#### *Dual task condition*

In the dual task condition, participants were required to perform the Sternberg memory task in addition to the flanker task (whose parameters remained the same). Participants were presented with a set of either four or seven consonants to be remembered over a delay period as described above for the Sternberg condition. Between 300–500 ms following presentation of the memory set, the flanker trials began. Nine flanker trials were presented. At 500 ms following the final flanker trial of the block, participants were presented with a probe item (a consonant) and responded with a button press to indicate whether this item was in the previous memory set. On half the trials the probe was a member of the memory set, on the other half, it was not. The probe trial terminated once a response was made. Each participant completed a total of 90 flanker trials in each of the 10 blocks (total: 900 flankers). The Sternberg task was randomly selected to have five sets of four items and five sets of seven items for each of the 10 blocks (total: 50 sets of 4; 50 sets of 7).

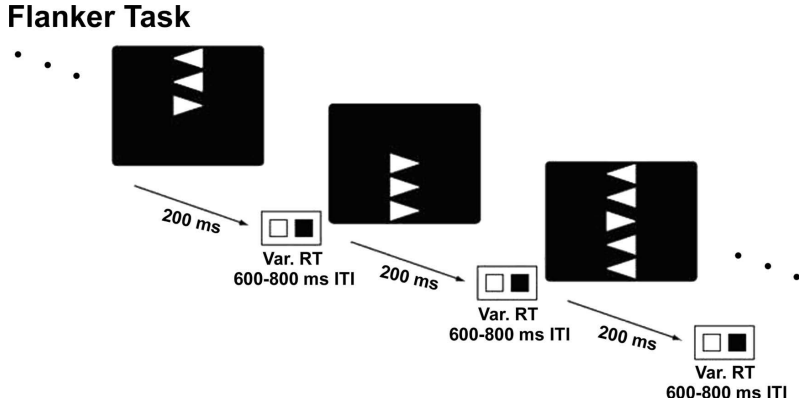


**FIGURE 1 | Flanker task design.** Participants responded to direction of the central arrow using a two-button response. Flanker arrows could be either congruent or incongruent and above, below, or both above and below the central arrow.

### EEG RECORDING

The EEG was recorded from participants using an SA Instrumentation amplifier and DataPAC 2000 software. The EEG was sampled at 256 Hz using an online low-pass filter of 100 Hz and a high pass of 0.1 Hz. Impedances were maintained below 10 kΩ. Electrodes were initially referenced online to the left mastoid. Eye artifacts (e.g., blinks, movements) were monitored with four EOG electrodes and corrected offline. Offline analysis was completed with EEGLAB (www.sccn.ucsd.edu/eeglab). Filtering was set with a low-pass at 20 Hz and the data were re-referenced to the average mastoid. The data were re-sampled to 250 Hz. Independent components analysis was used to extract out eye-blink and eye movements within the data. Individual ERP segmentation began 100 ms before, and continued 900 ms post-stimulus onset. All segments were baseline corrected and averaged. ERP segments were time locked to the onset of the flanker.

### STATISTICAL ANALYSIS

#### *Behavioral performance*

Behavioral analyses examined the effect of RT and accuracy using repeated measure ANOVAs. Only correct responses to the flanker trials were used in the analysis. The flanker data were analyzed using a 2 × 3 factor design: congruence (congruent or incongruent) × load (single flanker, set size 4, or set size 7). The Sternberg data were analyzed using a 2 × 2 factor design: load (single or dual) × set size (four or seven items). Follow-up paired *t*-test comparisons investigated significant interactions. Only correct responses were used in the RT analysis.

#### *Event-related potentials*

Electrophysiological analyses examined the P1 and P300 in the stimulus-locked waveform. Only trials with correct responses were used in the analysis. The P1 was identified as the first positive peak in the time window of 110–130 ms at electrodes O1 and O2. Mean amplitudes in the 110- to 130-ms interval were measured across both occipital electrodes. The P300 was identified as the large positive component that occurred between 350 and 600 ms. The ERP mean amplitude measures for P1 and P300 were then submitted separately to two-way ANOVAs that examined congruence (congruent or incongruent) × load (single flanker, set size 4, or set size 7).

## RESULTS

### BEHAVIORAL

#### *Flanker task*

For RTs, a main effect of congruence was found, indicating that participants were faster to respond to congruent flankers compared to incongruent flankers [$F(1,14) = 58.053$, $p < 0.001$; see **Figure 2A**]. Only a marginal effect was found for load [$F(2,28) = 2.679$, $p = 0.086$]. The trend is consistent with the observation that the fastest RTs occurred during the single flanker condition (411.5 ms) followed by the dual task condition with Sternberg set sizes of 4 (423 ms) and 7 (430 ms). The interaction between congruence and load was not significant ($p = 0.95$), indicating that the addition of a working memory task did not alter the flanker interference effect.

Overall accuracy in the flanker task was fairly high (mean = 91%). The main effect of congruence reflected the fact that accuracy was higher when flankers were congruent, relative to incongruent [$F(1,14) = 56.934$, $p < 0.001$]. In addition, a main effect of load suggests that responses were more accurate in the single task condition than when combined with a Sternberg set of four or seven [$F(2,28) = 5.780$, $p = 0.026$]. The main effects were followed by a significant interaction of congruence × load [$F(2,28) = 13.293$, $p < 0.001$]. Follow-up comparisons revealed that the flanker interference effect was greater in the dual task conditions. Responses were more accurate on incongruent trials in the single flanker condition compared to the dual task with set size 4 [$t(14) = 3.301$, $p = 0.005$] or set size 7 [$t(14) = 3.280$, $p = 0.005$; see **Figure 2B**]. There was no significant effect of load when the flankers were congruent [single flanker versus set size 4: $t(14) = 0.891$, ns; single flanker versus set size 7: $t(14) = 1.271$, ns; set size 4 versus set size 7: $t(14) = 1.096$, ns].

Additional correlation analyses were conducted to test whether a speed versus accuracy trade-off occurred. We expected that load might have affected the error rate, which in turn was inversely related to the speed of the response. The stimuli appeared at a very rapid rate and to adjust for a higher error rate, participants might have slowed down. To test this, we used Pearson correlations for

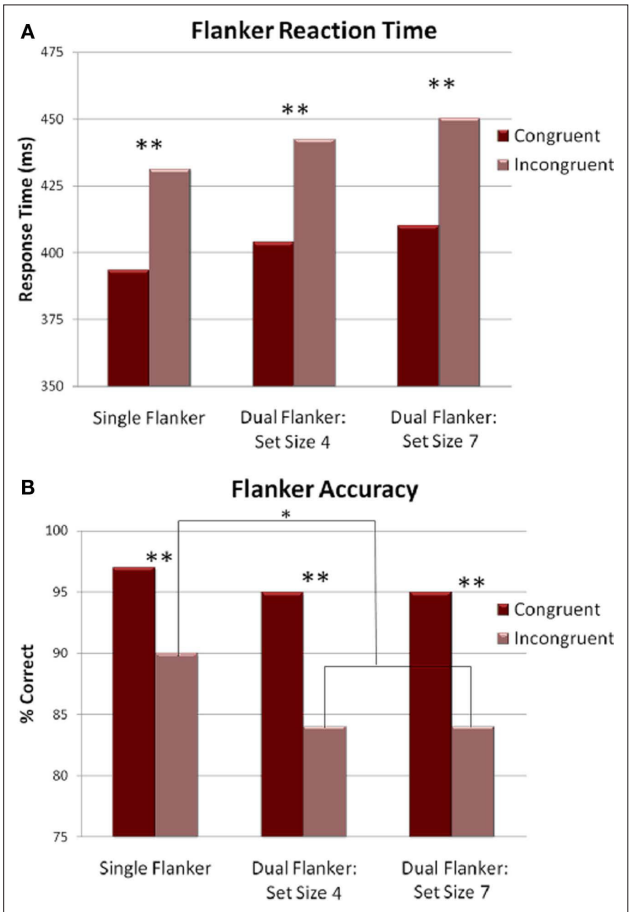


**FIGURE 2 | Behavioral results for the flanker task. (A)** RTs plotted for each condition. Responses on incongruent trials were slower than those on congruent trials for all conditions. **(B)** Accuracy plotted for each condition. Accuracy decreased in both dual task conditions on incongruent trials, compared to the single flanker task. $*p < 0.05$, $**p < 0.001$.

RT and accuracy for each of the load conditions. Results indicated that participants did make speed/accuracy trade-offs, but only in the most difficult conditions. A significant correlation was found for incongruent trials for set size 4 ($r = 0.519$, $p = 0.047$) and set size 7 ($r = 0.801$, $p < 0.001$), but not for single flanker. When the task became more difficult (i.e., incongruent flankers), longer RTs were associated with an increase in accuracy.

### *Sternberg task*

For RTs, a main effect of set size indicated that responses to the memory probes were significantly faster when there were only four items in the set as opposed to seven [$F(1,13) = 28.461$, $p < 0.001$]. There was neither a main effect of task ($p = 0.50$) nor an interaction ($p = 0.44$), which suggests that the addition of an attention task did not alter RTs to memory probes (see **Figure 3A**).

The analysis of accuracy on Sternberg trials revealed a significant main effect of load [$F(1,13) = 12.429$, $p = 0.003$] indicating that responses were more accurate when completing the Sternberg trials alone, compared to when the flanker trials intervened. The analysis also revealed a significant main effect of set size indicating that participants were more accurate when there were only four items in memory set compared to seven [$F(1,13) = 27.533$, $p < 0.001$]. This was followed by a significant interaction of load × set size [$F(1,13) = 24.548$, $p < 0.001$; see **Figure 3B**]. Follow-up comparisons indicated that accuracy declined in the dual task condition only when the set size contained seven items [$t(13) = -5.115$, $p < 0.001$]. Participants were significantly more accurate when responding to probes from set size 4 compared to set size 7 in both the single [$t(13) = -2.789$, $p = 0.015$] and dual task conditions [$t(13) = -6.585$, $p < 0.001$].

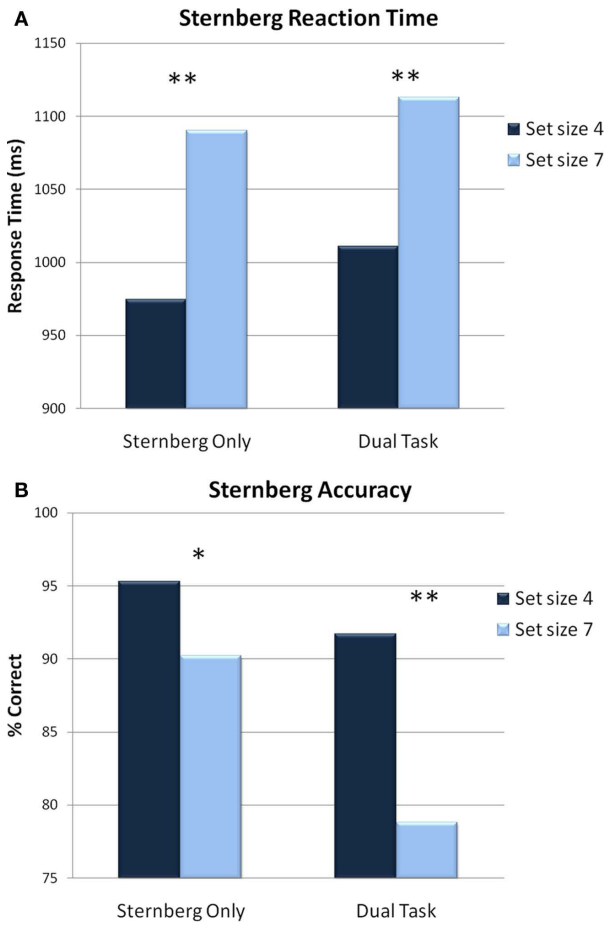


**FIGURE 3 | Behavioral results for the Sternberg task. (A)** RTs on Sternberg trials for each condition. Participants responded faster to probes from a set size of 4 compared to set size of 7. **(B)** Accuracy on Sternberg trials for each condition. Accuracy declined to probe items from a set size of 7 compared to a set size of 4. *$p < 0.05$, **$p < 0.001$.

## EVENT-RELATED POTENTIALS

### *P1*

The P1 was quantified across electrodes O1 and O2 as the most positive peak occurring between 110 and 130 ms after stimulus onset. The mean amplitude during this time window was averaged across both electrodes and analyzed in a two-way ANOVA. A significant main effect of load [$F(2,28) = 7.423$, $p = 0.007$] indicated that P1 amplitude decreased when the Sternberg task was included, relative to the single task condition (see **Figure 4**). P1 amplitude was significantly larger in the single flanker compared to the dual task conditions with either four [$t(14) = 2.893$, $p = 0.012$] or seven items [$t(14) = 3.21$, $p = 0.006$], whereas the latter two conditions did not differ from each other [$t(14) = -0.908$, ns]. There was neither a main effect of congruence [$F(1,14) = 0.008$, ns] nor a significant interaction of load × congruence [$F(2,28) = 0.536$, ns].

### *P300*

Mean amplitudes between 300 and 650 ms were examined with an initial three-way ANOVA including the midline electrodes (electrode: Fz, FCz, Cz, CPz, Pz, POz), congruence (congruent, incongruent), and load (single flanker, set size 4, set size 7) as factors. A significant main effect of electrode [$F(5,70) = 8.031$, $p < 0.007$] was found. The largest P300 amplitude was observed at CPz, which was the focus of subsequent analyses. A two-way ANOVA at CPz showed a main effect of congruence [$F(1,14) = 4.633$, $p = 0.049$] that indicated larger positive amplitudes to incongruent versus congruent trials. A marginally significant effect of load [$F(2,28) = 3.681$, $p = 0.073$] suggested that the single flanker condition elicited the largest amplitude response (7.01 μV), followed by the dual task conditions with set size 4 (5.984 μV) and set size 7 (5.4 μV). In addition, a significant interaction between load and congruence [$F(2,28) = 3.709$, $p = 0.04$] was observed. Follow-up comparisons revealed that incongruent flankers produced a larger P300 in the single task condition, compared to the dual task conditions with set size 4 [$t(14) = 2.178$, $p = 0.047$] or set size 7 [$t(14) = 2.798$, $p = 0.014$; see **Figure 5**].

## DISCUSSION

The current study tested the effects of working memory load on attentional control and conflict resolution using a dual task design. The results demonstrated that the concurrent task demands of maintaining items in working memory diminished the ability to attend to targets and ignore distractors in a flanker interference task. Incongruent flanker stimuli were more difficult to ignore when

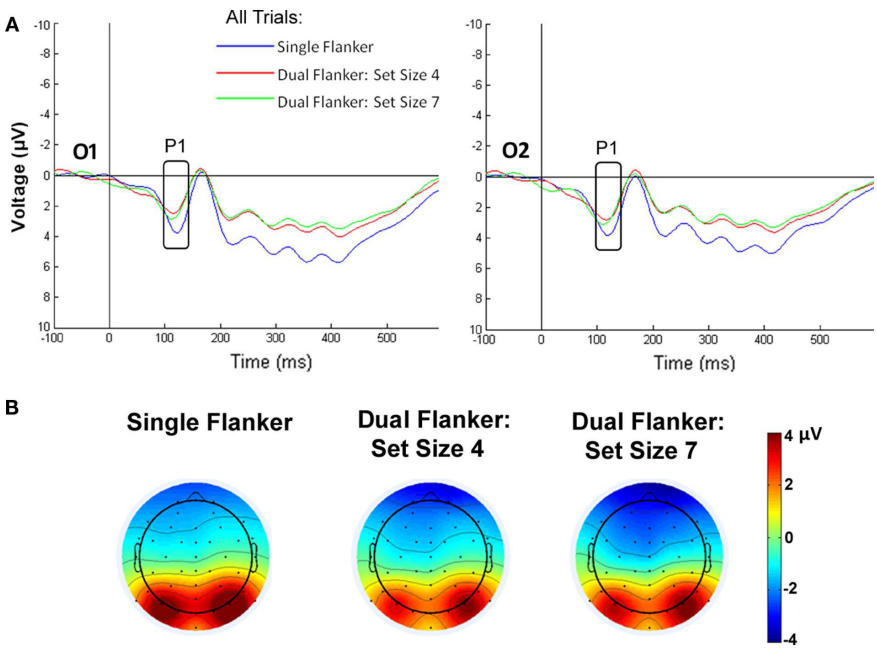


**FIGURE 4 | P1 in response to load. (A)** The dual task conditions significantly diminished P1 amplitude at electrode O1 and O2, compared to the P1 amplitude for the single task. **(B)** Topographic maps display the scalp voltage distribution at 120 ms, indicating that the P1 is located over both O1 and O2 electrodes for each task condition.

working memory load increased, as indicated by reduced behavioral accuracy and decreased P300 amplitude. This suggests that working memory is needed to filter out irrelevant information, selectively focus attention and resolve response conflict. Furthermore, the convergence of behavioral and ERP results supports the integral role of working memory in directing and regulating attentional selection, in support of the cognitive load theory (Lavie et al., 2004).

As observed in many prior studies, accuracy was lower when the flankers were incongruent relative to congruent (Eriksen and Eriksen, 1974; Kopp et al., 1996). This performance deficit was worsened when participants were required to maintain either four or seven items in working memory during the flanker task. Previous research has found slower RTs in flanker-type tasks when working memory load was high and distractors were incongruent (Lavie, 2005; Lavie and De Fockert, 2005). Although our current RT results did not show greater flanker interference with added working memory demands, the accuracy results indicated that incongruent distractors did cause greater interference when working memory was loaded. The lack of an RT interference effect may be due in part to the short trial and inter-trial durations. The flanker task was fast-paced, which led to a significant speed/accuracy trade-off in the dual task conditions.

Compared to working memory performance in the single task condition, accuracy in the dual task Sternberg decreased, but only for memory sets with seven items. This suggests that the dual task design produced deficits in working memory when attentional demands were instituted during the delay period, but only for the high load condition. The current results also suggest that divided attention is detrimental to working memory, especially under more difficult conditions (Kane and Engle, 2003). This is consistent with Gazzaley's (2011) recent review of the literature showing that as working memory load increases, attentional capacity decreases, and in turn, causes working memory performance to decline.

Event-related potential recordings provided evidence for electrophysiological changes associated with dual task processing. Both P1 and P300 showed significant decreases in amplitude in the flanker task when working memory demands were increased. Early changes in the P1 indicated that regardless of distractor congruity, initial visual processing was diminished when working memory was taxed. This decline in amplitude occurred regardless of the number of items held in working memory. The later P300 component also decreased significantly when working memory was loaded, but only for trials with incongruent flanker stimuli.

Previous research suggests that P1 generally increases in amplitude to targets appearing in an attended location and decreases to targets at an unattended location (Hillyard et al., 1998; Hopfinger et al., 2000; Luck et al., 2000). In the current study, attention was divided between the flanker stimuli and the contents of working memory during the dual task conditions. Coordination of dual task performance utilized resources typically involved in modulating early visual processing. Importantly, the early onset of the P1 effect suggests that top-down processes in PFC influence visual attention within 110–130 ms of stimulus presentation. Neuropsychological studies have provided direct evidence for this modulatory effect. Patients with lesions of PFC show reductions in early visual components, such as the N1 and N2 (Knight, 1997), the left lateralized N170 to words (Swick, 1998), and the P1 (Barceló et al., 2000; Yago et al., 2004). These lesion results suggest that PFC normally provides

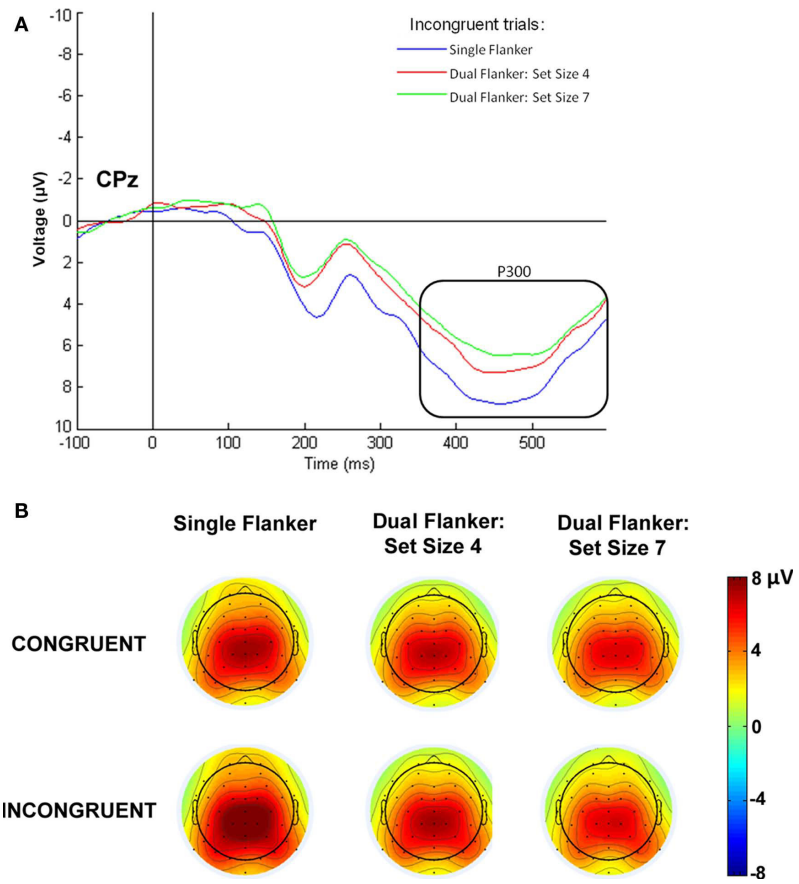


**FIGURE 5 | P300 to incongruent flankers in response to load. (A)** The P300 response significantly decreased to incongruent flanker stimuli in the dual task condition compared to the single task condition at electrode CPz. **(B)** Topographic maps display the scalp voltage distribution at 450 ms, showing the interaction of congruence by load.

an excitatory input to boost attentionally relevant processing in extrastriate cortex. Therefore, when working memory and dual task demands tax the PFC in healthy controls, it is likely that fewer resources are available to modulate the P1 response in extrastriate cortex. As other researchers have found that P1 decreases as a function of attention (Hillyard et al., 1998; Luck et al., 2000), our current findings suggest that attention decreases when items are maintained in working memory, and that this may be the result of less top-down activation from the PFC.

Previous fMRI results demonstrated an increase in activation in extrastriate regions when working memory load was high compared to low (de Fockert et al., 2001), a finding that has recently been extended to primary visual cortex (Kelley and Lavie, 2010). de Fockert et al. (2001) suggested that increased activity in visual cortex reflected difficulty in ignoring irrelevant stimuli. That is, visual regions were more active when working memory load was high and distractors were present (de Fockert et al., 2001). In the current study, P1 was not sensitive to distractor processing (i.e., no effect of flanker congruence). The difference between our results and those of de Fockert et al. (2001) may relate to the temporal resolution of the methods used. As mentioned before, fMRI provides good spatial resolution of brain activation to specific stimuli, but is unable to provide good temporal resolution. Thus, it is unknown whether the extrastriate activation reflects early or late changes in visual processing. In contrast, our findings suggest that within the first 100 ms, the response of visual cortex to attentionally relevant stimuli is diminished when items are maintained in working memory.

In contrast to the P1, the P300 component showed a decrement in the dual task conditions only when irrelevant stimuli were present (similar to performance accuracy). Previous reports have indicated that P300 amplitude decreases as a function of task difficulty (Picton, 1992; Garcia-Larrea and Cezanne-Bert, 1998; Wintink et al., 2001). In dual task conditions, P300 reflects the amount of resources available for the current task (Sirevaag et al., 1989; Singhal and Fowler, 2004), and P300 amplitude decreases in the secondary task as the difficulty of the primary task increases. As predicted, we observed a reduction in P300 amplitude on incongruent trials when working memory load increased. This is consistent with the notion that increased complexity of task demands caused greater distribution of attentional resources and therefore, a reduction in recruitment of the generators of the P300 (Wintink et al., 2001).

The interaction of load and congruity indicated that demands on working memory influenced the P300 amplitude to incongruent flankers only. As suggested by Lavie and colleagues (de Fockert and Lavie, 2001; Lavie et al., 2004; Lavie, 2005; Lavie and de Fockert, 2005), working memory functions to selectively focus attention on the target and reduce the intrusion of irrelevant distractors. The current P300 findings support this hypothesis and suggest that interference from incongruent flankers was more difficult to process when working memory capacity was full (de Fockert et al., 2001). Controlling attention during multiple tasks requires the frontal executive component to coordinate planning and attention to goal-relevant stimuli (Garcia-Larrea and Cezanne-Bert, 1998). Although lesions studies have suggested that the P300 recorded in simple target detection tasks does not have neural sources in PFC (Knight, 1997), P300 amplitude reductions have been observed in PFC patients during more difficult categorization tasks (Swick, 1998). Therefore, the decrease in P300 amplitude in the dual task conditions could reflect a decline in frontal-dependent measures of attentional control (Garcia-Larrea and Cezanne-Bert, 1998).

One limitation of the results was the inclusion of flanker arrows above, below, and both above and below the target arrow. The number of flankers in the display may have contributed to a perceptual load effect. According to Lavie et al. (2004) increasing perceptual load (number of items in the display) reduces the amount of interference caused by distractors. In contrast, increasing cognitive load causes greater interference in processing distractors (Lavie et al., 2004). The purpose of the current study was to examine the effects of cognitive load on attentional processing and ERP components. Flankers located both above and below the central target arrow could be considered a greater perceptual load than flankers either below or above the target arrow. In order to reduce the effect of perceptual load and only examine cognitive load, we collapsed across arrow location to selectively examine cognitive load only. Future studies should examine the electrophysiological changes associated with perceptual load processing and the interaction of perceptual load and cognitive load on attention.

## CONCLUSION

The present study illustrates the detrimental effects of dual task processing and cognitive control. High working memory load interfered with the attentional control network, especially when attention was needed to filter out irrelevant distractors. Our findings extend the work of Lavie and colleagues (de Fockert and Lavie, 2001; Lavie et al., 2004; Lavie, 2005; Lavie and de Fockert, 2005) by revealing the time-course of load effects on the brain regions supporting visual attention and conflict resolution. The early extrastriate P1 response was sensitive to increases in cognitive load regardless of distractor congruity. We suggest that working memory demands decreased top-down modulatory influences from PFC as early as 100 ms. The later P300 response was sensitive to both increased cognitive load and the presence of distracting flanker stimuli. We suggest that the decrease in P300 amplitude reflects the diminished availability of resources to selectively focus attention and resolve response conflict. The present findings support and extend the evidence for the necessity of working memory in resolving response conflicts and attention. Future studies in patients with PFC lesions, or lesions in white matter tracts connecting frontal and posterior association cortices, will be helpful in understanding the importance of frontal projections on top-down attention processing and cognitive control.

## ACKNOWLEDGMENTS

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# Post-traumatic stress disorder is associated with limited executive resources in a working memory task

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**Background:** The goal of the current experiment was to examine the extent of central executive impairments in patients with post-traumatic stress disorder (PTSD). A dual-task design was used to determine if impairment in working memory was linked to executive control limitations by examining performance on a memory task alone and in conjunction with a secondary attention task presented during the maintenance period.

**Methods:** Participants performed a Sternberg memory task in which either one or four letters were presented. After a delay, participants indicated whether or not a probe letter was a member of the previous memory set. In a single-task condition, the Sternberg task was performed alone. In a dual-task condition, the delay was filled with an arrow flanker task in which participants responded to a central arrow surrounded by distractors.

**Results**: Behavioral analysis found a significant group by task interaction, indicating that PTSD patients were less accurate on the working memory task than the controls, especially in the dual-task condition. Electrophysiological results indicated that both the PTSD group and the controls showed similar brain patterns from 300 ms to 500 ms when discriminating old and new probes in the single-task condition. However, when taxed with the additional flanker task during the maintenance period, the ERPs of the PTSD group no longer differentiated old and new probes.

**Conclusions:** The lack of differentiation in the ERP reflects impaired WM performance under more difficult dual-task conditions. Exacerbated difficulty in performing a WM task with concurrent task demands suggests limited executive control resources in PTSD.

## Introduction

Individuals with post-traumatic stress disorder (PTSD) often show impairments in coordinating, inhibiting, and monitoring cognition and behavior (Koso & Hansen, 2006; Leskin & White, 2007; Swick et al., 2012; Vasterling et al., 2012). These limitations in executive control can lead to impairments in multiple aspects of cognition. Executive control coordinates and manipulates information held in working memory, switches attention from one representation to another, inhibits pre-potent responses, maintains sequences of events, and monitors performance (Kosslyn & Smith, 2007). However, the effects of PTSD on executive control have not been as consistently documented as the well-known difficulties in regulating emotional memory and fear learning (e.g., Rauch, Shin, & Phelps, 2006). Some studies have reported deficits in working memory (WM) and attention in PTSD (Elzinga & Bremner, 2002; Koso & Hansen, 2006; Leskin & White, 2007; Vasterling et al., 1998), while other studies have shown little to no impairment in performance (Golier et al., 1997; Neylan et al., 2003; Brenner et al., 2010). The current experiment set out to determine if cognitive impairment in WM is linked to executive control limitations by examining performance on a WM task alone and when a secondary attention task was performed during the maintenance period. Exacerbated difficulty while performing a WM task with concurrent task demands would suggest executive control dysfunction in PTSD rather than a general decline in memory (Baddeley, 1996).

The severity of PTSD symptomatology is often related to cognitive dysfunction, specifically to a decline in attentional control and memory performance (Bremner et al., 1993; Drag et al., 2012; Elzinga & Bremner, 2002; Vasterling et al., 1998, 2012). Bremner et al. (1993) found a significant decline in both immediate and delayed recall in patients with PTSD compared to military controls using the Wechsler Memory scale. The impairment in WM performance was

strongly correlated with symptom severity of re-experiencing the traumatic event (Elzinga & Bremner, 2002). In addition, other studies indicate that re-experiencing is significantly related to impairments in inhibitory control (Swick et al., 2012; Vasterling et al., 1998). Within-subject variability can be observed in PTSD patients with inconsistent cognitive performance, and some researchers have suggested this may be related to fluctuating levels of attention and concentration (Neylan et al., 2003). The ability to focus on the task at hand is related to executive control, and inconsistent task performance may be an indicator of executive dysfunction (Stuss et al., 2003). The prefrontal cortex is thought to be critical for efficient functioning of executive control (McDowell et al., 1997; Smith et al., 1998; Wager & Smith, 2003). Therefore, manipulating the degree of executive control may be one way to uncover cognitive impairment in PTSD patients. Indeed, other research has suggested that PTSD is related to frontal lobe dysfunction because performance on certain tasks is similar to performance of patients with frontal lobe injury, specifically on memory tasks (Vasterling et al. 1998). Patients with frontal lobe damage may perform well on certain tasks, specifically those that do not require coordinating performance, but are unable to coordinate multiple processes as evidenced by declines in dual-task performance (Baddeley, 1996; Dreher et al., 2008). Likewise, cognitive deficits in traumatic brain injury (TBI) patients are more pronounced on complex, novel tasks and during dual-task performance (McDowell et al., 1997). In a similar fashion, cognitive difficulties in patients with PTSD might not necessarily be apparent when testing only one cognitive domain, but might instead be more prominent in tasks that require coordination of multiple elements. However, no studies have examined dual-task performance in PTSD. Here, we focus on WM retrieval and how it is affected by the performance of a demanding visual attention task during the retention interval.

To determine the nature of the neurophysiological changes that might underlie any behavioral deficits in PTSD patients, we also examined event-related potentials (ERPs) to WM retrieval and how the ERPs might be affected by the secondary task. Alteration of a relatively early electrophysiological component in the patients might be indicative of problems with item recognition, while later ERP changes could reflect difficulties with decision or post-retrieval monitoring processes (Wilding & Herron, 2006; Folstein & Van Petten, 2011). Previous ERP studies have used an "oddball" task to examine abnormalities in target detection and context updating in PTSD patients (Galletly et al., 2001; Javanbakht et al., 2011; Karl et al., 2006; Veltmeyer et al., 2009). The majority of papers have reported an attenuated P300 response to target stimuli (Galletly et al., 2001; Veltmeyer et al., 2009). However, performance on neuropsychological measures of WM is not correlated with the amplitude or latency of the P300 (Walhovd & Fjell, 2001). Therefore, a new approach is needed to examine electrophysiological changes more closely related to WM deficits.

A specific neural marker of memory retrieval processes is the ERP old/new effect. This electrophysiological response consists of a positive shift in the waveform to previously presented items that are correctly recognized, relative to new items that are correctly rejected (Rugg & Curran, 2007). Although typically examined using experimental designs such as study/test list learning (Rugg & Doyle, 1992; Smith, 1992) and continuous recognition (Friedman, 1990; Swick & Knight, 1997), the old/new effect has also been examined using WM and Sternberg tasks (Tays et al., 2008, 2011). In those studies, an array of letters or words was presented, followed after a delay by a probe stimulus. A probe that was correctly identified as being contained within the array ("old") elicited a greater positivity from approximately 350 to 600 ms than a probe that was not in the array ("new").

Thus far, no studies have examined ERP old/new effects in individuals with PTSD, either under single- or dual-task conditions. In addition to examining verbal WM performance, the present study incorporated a distracting secondary task to tax executive control processes while maintaining a smaller or larger memory set. We predicted that PTSD patients would show a disproportionate decline in WM performance in the dual-task condition. Electrophysiological measures were expected to reflect this decline in performance by showing a reduction in the amplitude of the old/new effect in the dual-task condition, suggesting that the secondary task would disrupt WM retrieval processes in PTSD.

## Methods

Participants

Participants were 18 Iraq and Afghanistan combat Veterans diagnosed with PTSD (17 male, 1 female) and 16 demographically matched control Veterans (15 male, 1 female). One combat Veteran in the PTSD group was unable to complete the experiment and was subsequently dropped from analysis leaving the PTSD group at n=17 (16 male, 1 female). Fourteen of the participants with PTSD had attended a clinic for traumatic brain injury (TBI); however, all participants reported no history of TBI involving loss of consciousness greater than five minutes (Shin et al., 2009), or any other pre-existing neurological disease. PTSD diagnosis was confirmed via review of VA electronic medical charts. Individuals with PTSD and military controls did not significantly differ in age (PTSD: mean age 33 $\pm$ 7 years; Controls: mean age 36 $\pm$ 7 years), ($F(1,31) = 1.46$, $p=0.24$). However, there was a significant group difference for education (PTSD: mean years of education: 13.68 $\pm$ 1.10; Controls: 14.94 $\pm$ 1.95), ($F(1,31) = 10.37$, $p=0.003$). Previous work in our lab with a larger sample of this population showed no significant relationship between education or intelligence and inhibitory control (Swick et al.,

2012). Both the PTSD and control groups were enrolled into the study in parallel.

None of the enrolled participants reported significant substance abuse or a history of other psychological disorders, excluding depression, due to the high comorbidity with PTSD in this population (Seal et al., 2008). The Institutional Review Board of the VA Northern California Health Care System approved the experimental protocol, and all participants gave informed consent prior to beginning the experiment. They were paid for transportation expenses plus $20 per hour for their participation. All participants had been previously enrolled in an ongoing research project.

Stimuli and Tasks

*Single-Task Condition (Sternberg Memory Task):* In the single-task condition, participants were required to perform a Sternberg memory task. Participants were seated in a darkened, sound-attenuated room and were instructed to fixate at the center of a screen, and asked to blink as little as possible. Participants were shown either one consonant (presented for 2000 ms) or a set of four consonants (presented for 3500 ms), which they were asked to remember. After a delay of 8500 ms, another consonant was presented (the probe). Participants responded with a button press to indicate whether the probe was part of the previous memory set (old) or whether the probe was not part of the memory set (new). For each trial, the set size (one or four) as well as the probe type (old or new) was determined randomly with equal probabilities. There were ten blocks of ten trials each, for a total of 100 trials.

*Dual-Task Condition (Sternberg Memory Task +Arrow Flanker):* In the dual-task condition, participants were required to perform an additional arrow flanker task during the delay interval of the Sternberg memory task just described. Nine flanker trials began 300 to 500 ms following the presentation of each Sternberg memory set. Participants were instructed to respond

with a button press to indicate, as quickly and accurately as possible, whether each central arrow pointed to the left or the right. Flanking arrows, positioned either above, below, or both above and below the central arrow, could point in either the same (congruent) direction (40 percent of trials) or different (incongruent) direction (60 percent of trials). Each flanker stimulus was presented for 200 ms, with the next trial beginning 300 to 500 ms after a response was made. If there was no response, the next trial began after 900 ms. The Sternberg probe was then presented 500 ms following the final flanker trial, and participants responded with a button press to indicate whether this item was in the previous memory set. Other parameters were as described above. Each of the ten blocks contained ten Sternberg trials, each with nine flanker trials embedded during each delay interval, for a total of 100 Sternberg trials and 900 arrow flankers. A single-task version of the arrow flanker was also presented during the session, which will be reported elsewhere. Each participant completed all three tasks, with task order counterbalanced. The total test time was approximately two hours.

EEG Recording

Continuous EEG was recorded from 64 scalp electrodes and two electrodes placed on the left and right mastoids using the ActiveTwo Biosemi electrode system. Four electrodes placed laterally and below the right and left eyes recorded blinks and eye movements. The EEG was sampled at 512 Hz. Off-line analysis was completed using Brain Vision Analyzer software. Data were re-referenced to the average of the mastoid electrodes and bandpass filtered from 0.1 to 30 Hz. The EEG was segmented for each trial from 100 ms pre-stimulus to 900 ms post-stimulus onset. EEG was corrected for blinks; eye movements and extraneous artifacts exceeding 150 microvolts were rejected.

Statistical Analysis

*Behavioral Performance:* Behavioral analyses examined reaction time (RT) and accuracy using repeated measure ANOVAs. Only correct responses to Sternberg probes were used in the RT analysis. The RT data for the Sternberg were analyzed using a 2 x 2 x 2 x 2 design with within-subjects factors Task (single or dual), Set Size (one or four), and Probe (old or new), and between-subjects factor Group (PTSD or control). The accuracy data analysis examined the percentage of correct responses using the same factor design as the RT analysis.

*Electrophysiological Analysis:* Experimental effects on ERPs time-locked to the onset of the Sternberg probe were analyzed by taking the mean amplitude of six midline electrodes over time windows of 300-400 ms, 400-500 ms, 500-600 ms, and 600-700 ms, with the factors Task (single or dual), Set Size (one or four), Probe (old or new), Electrode (Fz, FCz, Cz, CPz, Pz, or POz), and Group (controls or PTSD) for correct responses only. These intervals were selected to capture the sustained old/new effects of the Task manipulation that were observed beginning around 300 ms after presentation of the probe. To ensure that each averaged ERP represented a sufficient number of artifact-free segments per participant (mean > 40, minimum > 20), effects of Set Size were examined in analyses that collapsed across Probe, and effects of Probe were examined in analyses that collapsed across Set Size.

## Results

Behavioral Results

Individuals with PTSD were less accurate than controls on the Sternberg WM task, and their performance was disproportionately impaired in the dual-task condition (Figure 1). This was supported by a main effect of Group [$F(1,31)=5.55$, $p=0.03$] and a Task by Group

interaction [$F(1,31)=4.42$, $p=0.04$]. The PTSD patients were not significantly different from controls in the single-task condition [$F(1,31)=2.49$, $p=.12$] but were significantly less accurate on the Sternberg task in the dual-task condition [$F(1,31)=6.42$, $p=0.02$], when the demanding flanker task occurred during the WM delay (Figure 1). Accuracy scores in the PTSD patient group dropped from 93.7% in the single task to 86.7% in the dual task [$F(1,16)=13.49$, $p=.002$]. The controls also showed a decline in accuracy, yet the decrease in performance was smaller (single task: 96.5%; dual task: 93.9%), [$F(1,15)=11.79$, $p=.004$]. In addition, all participants were less accurate in the dual task compared to the single task, and for new probes compared to old probes (Table 1), as indicated by significant main effects of Task [$F(1,31)=20.81$, $p<0.0001$] and Probe [$F(1,31) = 8.97$, $p=0.005$].

In contrast, the two groups did not differ in their RTs to the memory probe [$F(1,31)=1.44$, $p=.24$], nor did Group interact with Task ($p=.19$), Set Size ($p=.16$), or Probe ($p=.45$). Only significant main effects of Task [$F(1,31)=42.69$, $p<0.0001$], Set Size [$F(1,31)=120.80$, $p<0.0001$], and Probe [$F(1,31) = 5.90$, $p=0.02$] were observed (Table 1). Responses were faster in the single task than in the dual task, faster for set size one than for set size four, and faster for old probes than for new probes.

Spearman correlation analyses were used to examine the relationship between accuracy and scores on the PCL. Both re-experiencing and avoidance/numbing, but not hyperarousal, were significantly correlated with accuracy in the dual task condition (re-experiencing: *rho* = -0.388, p=0.028; avoidance/numbing: *rho* = -0.369, p=0.037; hyperarousal: *rho* = -0.312, p=0.082).

ERP Results

Beginning with the 300-400 ms window, large effects of Task began to emerge. ERPs were more positive in the dual-task condition compared to the single-task condition across all participants [$F(1, 31)=37.6$, $p<.001$]. This Task effect interacted with Electrode [$F(5, 155)=32.4$, $p<.001$], being largest at Cz and FCz. Further, ERPs to old probes were more positive in amplitude than those to new probes [$F(1, 31)=9.6$, $p=.004$]. This Probe effect interacted with Task and Electrode [$F(5, 155)=2.8$, $p=.05$], such that Probe effects were larger at Cz and FCz in the single task, but were more uniform in the dual task. Finally, the analysis including the factor Set Size confirmed that ERPs to set size one were more positive than those to set size four [$F(1, 31)=6.2$, $p=.02$]. This Set Size effect interacted with Electrode [$F(5, 155)=3.5$, $p=.03$], being largest at Fz.

The major finding was that the PTSD patients did not show any differences between ERPs to old and new probes in the dual task condition. This was supported by a three-way interaction between Task, Probe, and Group [$F(1, 31)=12.3$, $p=.001$]. This interaction was explored in follow-up analyses conducted separately on the single- and dual-task conditions. For the single task alone, a strong effect of Probe was observed [$F(1, 31)=12.5$, $p=.001$], with more positive measurements for old probes. This effect did not interact with Group for the single task [p=.36] (Figures 2 and 3). For the dual task alone, a main effect of Probe [$F(1, 31)=4.0$, $p=.05$] interacted with Group [$F(1, 31)=5.3$, $p=.03$]. This interaction was in turn followed up in separate analyses for each Group, which showed that, in the dual-task condition, controls demonstrated a significant effect of Probe [$F(1, 15)=7.6$, $p=.02$], consistent with single-task performance where old probes produced a more positive shift in the waveform (Figure 2). However, individuals with PTSD did not show any distinction between old and new probes in the dual-task condition

[*p*=.81] (Figure 3).

Largely similar effects and interactions were observed for the 400-500, 500-600, and 600-700 ms window, as shown in Table 2. The main effect of Task, and its interaction with Electrode, remained significant across all the later time windows. The critical interaction between Task, Probe, and Group remained significant through 600 ms, after which it reduced to a trend (Table 2). Follow-up analyses demonstrated a consistent pattern, such that the interaction was driven by the performance of the PTSD group, who demonstrated a statistically flat effect of Probe during the dual-task condition.

Next, we examined the relationship between the severity of PTSD symptoms and the magnitude of the ERP effect related to memory retrieval. PCL-M subscores were correlated with the mean voltage difference between old and new items between 300-400 ms at electrode Cz. Re-experiencing showed a significant negative correlation with the ERP old/new effect in the dual task condition (Re-experiencing: *rho* = -0.536, p=0.002), while avoidance/numbing showed only a trend (*rho* = -0.342, p=0.055) and hyperarousal was not significant (*r*= -0.322, p=0.72).

## Discussion

PTSD patients showed declines in both recognition accuracy and the ERP old/new effect during the dual task condition. In contrast, PTSD patients performed similarly to controls and showed comparable electrophysiological differences between old and new probes in the single-task condition. These novel findings suggest that a limitation in central executive resources contributed to the patients' impaired performance in the dual-task condition. The ERP results indicate that working memory processes were intact in the patients, but the addition of a secondary task during the retention interval interfered with item recognition.

Baddeley (1996) proposed that deficits in the central executive were seen in patients who typically showed behavioral difficulties with concentration, inhibition and attention, specifically when coordinating more than one task at a time. In this case, patients with Alzheimer's disease performed similar to controls on working memory alone but showed a significant decline in accuracy with a concurrent attention task. This finding signified that the disruption of performance was related to executive control dysfunction and not necessarily impairment in verbal working memory capacity (Baddeley et al., 1986, 1991). Our current findings show a similar pattern of intact performance on working memory when tested in isolation, yet significant decreases in accuracy when performed in a dual-task condition. This pattern of performance therefore suggests that individuals with PTSD show central executive deficits because of their impaired multitasking performance, compared to relatively preserved performance on the single task.

One explanation of this pattern is that the patients were able to maintain the items in working memory when there was no distraction, but had difficulties with sharing the cortical resources needed to resolve interference in the flanker task. Previous findings have suggested that patients with PTSD rely more strongly on repeating the last few items on a word list as indicated by an increase in recency scores on memory tests compared to controls (Johnsen & Asbjornsen, 2009). If patients with PTSD were more reliant on a rote encoding strategy in the current task, and less efficient at maintaining the stimuli in a longer-term storage that would be less susceptible to interference, then the secondary task could have reduced their ability to explicitly rehearse the encoded information. This view is supported by theories suggesting that PTSD symptoms can cause deficits in learning and memory due to an inability to disengage from trauma-related memories, even on neutral, non-trauma related tasks (Vasterling et al., 1998). In

other words, the traumatic memories occupy a central portion of working memory, and an added cognitive task has to compete with the processing of emotionally charged material.

Our interpretation of the behavioral results need not be reliant of the concept of a unitary central executive, which is not endorsed by Baddeley (2000). Indeed, another conception of executive control is that its different functions are fractionated and anatomically dissociable via neuroimaging and neuropsychological studies (Stuss, 2011). In addition, latent variable analysis has differentiated working memory updating from task switching and response inhibition, which are considered separate executive functions (Miyake et al., 2000). Of these, task switching seems closest to dual task performance, but this can differ greatly based on experimental design and task requirements. Examining the behavior alone will not differentiate these specific subgroups of WM processes. Therefore, we also used ERPs to investigate the spatiotemporal dynamics of WM.

The early onset of the ERP deficit in the patients suggests that their decreased accuracy was a direct result of retrieval difficulties in the dual-task condition, as opposed to problems with later decision processes. Accurate recognition of an item that was previously encoded, compared to correct rejection of an item that was not previously encoded, is generally reflected as a positive shift in the ERP waveform starting around 300 ms (Rugg & Curran, 2007). The two groups showed comparable ERP effects from 300 ms to 500 ms when distinguishing between old and new probes in the single-task condition, similar to previous reports on the ERP old/new effect in working memory tasks in controls (Danker et al., 2008; Tays et al., 2011). However, when taxed with an additional flanker task during the maintenance period, the PTSD group no longer produced any ERP differences between old and new probes. This is generally consistent with Weber et al.'s (2005) study examining WM in PTSD patients using a variable target WM

task. ERPs associated with WM updating showed a diminished positive wave in PTSD patients starting around 300 ms in the frontal and parietal regions. Weber et al. (2005) suggested that diminished ERP components from 300 to 900 ms reflected abnormal frontal and parietal activations in patients with PTSD. Specifically, the authors argued that reductions in both the frontal and parietal region suggest that patients with PTSD have difficulties integrating information into WM (Weber et al., 2005). In the current study, differences between the PTSD group and the control group was found in the frontal-parietal network but only for the ERPs associated with distinguishing old versus new items under the dual task condition. Our findings extend previous reports by Weber and colleagues and suggest that dual-task performance exacerbates WM difficulties often found in PTSD patients.

The working memory deficit observed in dual-task conditions is similar to findings from patients with frontopolar cortex lesions (Dreher et al., 2008). Dreher et al. (2008) found that the extent of frontopoloar damage was correlated with diminished performance in the multitasking condition. Indeed, previous reports have specifically compared WM deficits in patients with PTSD to patients with frontal lobe damage (Weber et al., 2005; Vasterling et al., 1998). Knight and colleagues (1998, 1999) have observed diminished ERPs in patients with frontal lobe damage when updating events in WM. Our current findings also suggest diminished activation distributed in both the frontal and parietal lobe in WM updating. However, our findings are specific for the dual-task condition. This result suggests that abnormal distribution of frontal inhibition networks and parietal activation necessary to update WM are already functioning at a limited capacity in patients with PTSD. Results from this study show that PTSD patients can differentiate and update WM when the task is simple and there are few demands (only 1 or 4 items to recall). However, the patients show an inability to integrate this information when taxed

with an additional task as reflected in the lack of frontal and parietal activation during the old/new ERP recognition waveform.

The deficits in the dual-task condition cannot be attributed solely to task difficulty, because there was no interaction with WM set size. All participants showed increased response times to probes when maintaining a larger set size compared to a smaller set size. Although we expected set size to affect patient performance, our results instead suggest that significant WM impairment was observed only when coordinating more than one task, and was not caused by a general decline in WM capacity, at least for set sizes of one versus four items. Many previous studies have associated WM impairment with PTSD, but have usually used immediate free recall tests, such as CVLT, which are more difficult and typically require more than four items to be maintained in WM (for review see Johnsen & Asbjornsen, 2008). Future studies using dual-task designs may consider increasing the set size to determine whether an interaction between set size and task exists.

One limitation of the present study is the lack of a distractor condition in which participants passively view arrow flanker stimuli during the maintenance period. The current findings are unclear as to whether the disruption in WM performance was due to performance of the secondary flanker task or to the presence of visual distractors. Nonetheless, resistance to external distraction is also considered an executive component of WM (Gazzaley, 2011; Nee et al., 2012). Future studies including passive presentations of visual distractor stimuli will be critical in evaluating the extent of cognitive impairments using a dual-task design.

## Conclusions

Impairments in executive control have great clinical importance because even subtle deficits can influence coping style and cognitive reappraisal strategies (Vasterling & Verfaellie,

2009). Previous results indicate that dual-task performance is reflective of real-world functioning (McDowell et al., 1997). Limitations in executive processing may contribute to the inability of individuals with PTSD to disengage from traumatic memories (re-experiencing) and to modulate emotional responses (hyperarousal). These in turn may lead to withdrawal from situations in which executive control is likely to fail (avoidance and numbing) (Aupperle et al., 2012). The dual-task design presented here is a useful experimental representation of the real-world multitasking deficits associated with PTSD, and may prove important in evaluating effectiveness of rehabilitation treatments.

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Table 1. Accuracy (percent correct ± SEM) and reaction time (mean ± SEM, in msec) for the controls and the participants with PTSD.

**Accuracy**

Single Task

| | Load 1 old | Load 1 new | Load 4 old | Load 4 new |
|---|---|---|---|---|
| Controls | 98.0 ± 0.6 | 95.6 ± 1.3 | 97.4 ± 1.0 | 94.5 ± 1.1 |
| PTSD | 93.9 ± 1.8 | 92.7 ± 2.8 | 97.1 ± 1.3 | 91.1 ± 1.9 |

Dual Task

| | Load 1 old | Load 1 new | Load 4 old | Load 4 new |
|---|---|---|---|---|
| Controls | 96.6 ± 1.3 | 93.4 ± 2.0 | 95.0 ± 1.4 | 90.6 ± 1.4 |
| PTSD | 90.2 ± 3.7 | 86.1 ± 3.3 | 89.3 ± 2.5 | 81.3 + 3.8 |

**Reaction Time**

Single Task

| | Load 1 old | Load 1 new | Load 4 old | Load 4 new |
|---|---|---|---|---|
| Controls | 769 ± 46 | 882 ± 60 | 1049 ± 60 | 1135 ± 95 |
| PTSD | 978 ± 82 | 1102 ± 91 | 1216 ± 84 | 1210 ± 85 |

Dual Task

| | Load 1 old | Load 1 new | Load 4 old | Load 4 new |
|---|---|---|---|---|
| Controls | 1027 ± 79 | 1119 ± 73 | 1279 ± 72 | 1360 ± 92 |
| PTSD | 1141 ± 91 | 1206 ± 110 | 1391 ± 87 | 1394 + 115 |

Table 2

| | 100-120 ms | 300-400 ms | 400-500 ms | 500-600 ms | 600-700 ms |
|---|---|---|---|---|---|
| Task | $F$=5.1, $p$=.03 | $F$=37.6, $p$<.001 | $F$=64.6, $p$<.001 | $F$=30.4, $p$<.001 | $F$=15.8, $p$<.001 |
| Task x Electrode | n.s. | $F$=32.4, $p$<.001 | $F$=38.0, $p$<.001 | $F$=14.6, $p$<.001 | $F$=11.6, $p$=.001 |
| Probe | n.s. | $F$=9.6, $p$=.004 | $F$=5.2, $p$=.03 | n.s. | n.s. |
| Task x Probe | $F$=7.5, $p$=.01 | n.s. | $F$=7.3, $p$=.01 | n.s. | n.s. |
| Task x Probe x Electrode | n.s. | $F$=2.8, $p$=.05 | $F$=3.2, $p$=.03 | $F$=2.5, $p$=.08 | n.s. |
| Set Size | n.s. | $F$=6.2, $p$=.02 | $F$=7.1, $p$=.01 | $F$=3.1, $p$=.09 | $F$=8.1, $p$=.008 |
| Set Size x Electrode | n.s. | $F$=3.5, $p$=.005 | $F$=4.1, $p$=.01 | n.s. | $F$=2.7, $p$=.07 |
| Group | $F$=4.4, $p$=.05 | n.s. | n.s. | n.s. | n.s. |
| Probe x Group | n.s. | n.s. | $F$=3.2, $p$=.08 | $F$=4.0, $p$=.05 | $F$=5.2, $p$=.03 |
| Task x Probe x Group | n.s. | $F$=12.3, $p$=.001 | $F$=6.0, $p$=.02 | $F$=5.0, $p$=.03 | $F$=3.2, $p$=.08 |
| Probe, single task | $F$=5.0, $p$=.03 | $F$=12.5, $p$=.001 | $F$=13.4, $p$=.001 | n.s. | n.s. |
| Probe x Group, single task | n.s. | n.s. | n.s. | n.s. | n.s. |
| Probe, dual task | n.s. | $F$=4.0, $p$=.05 | n.s. | n.s. | n.s. |
| Probe x Group, dual task | n.s. | $F$=5.3, $p$=.03 | $F$=6.3, $p$=.02 | $F$=7.9, $p$=.009 | $F$=8.6, $p$=.006 |
| Probe, dual task, controls | -- | $F$=7.6, $p$=.02 | $F$=5.1, $p$=.04 | $F$=4.9, $p$=.04 | $F$=5.8, $p$=.03 |
| Probe, dual task, PTSD | -- | n.s. | n.s. | $F$=3.2, $p$=.09 | $F$=3.4, $p$=.08 |

Figure Captions

Figure 1: Mean percent correct responses to Sternberg probe items, as a function of Task (single, dual) and Group (controls, PTSD). Individuals with PTSD were less accurate than controls were at classifying Sternberg probes as old vs. new, particularly for the dual task.

Figure 2: Event-related potentials time locked to the onset of the Sternberg probe item, as a function of Task (single, dual), Electrode (6 midline electrodes), Probe (old, new), and Group (controls, PTSD). The ERP old/new effect – the relatively positive shift for previously presented (old) probes that are correctly recognized, relative to new probes that are correctly rejected – was observed beginning at 300 ms for both groups in the single task condition, but only for the controls in the dual task condition.

Figure 3: Topographic plots illustrating the old-new difference wave as a function of Task (single, dual) and Group (controls, PTSD). More positive measurements for previously presented (old) probes, relative to new probes, are indicated by warmer colors.

Figure 1.

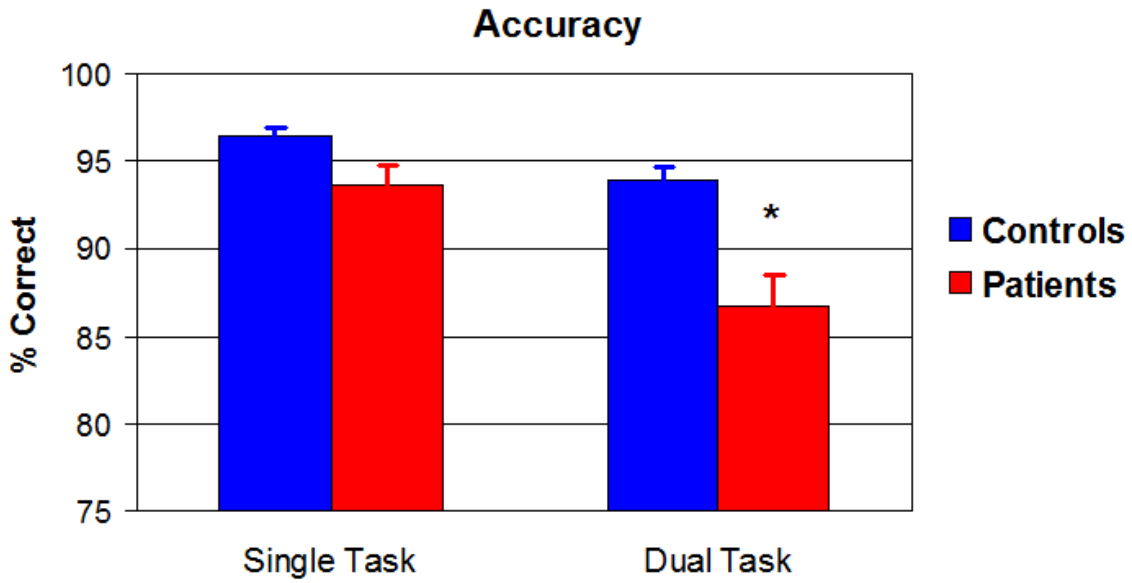
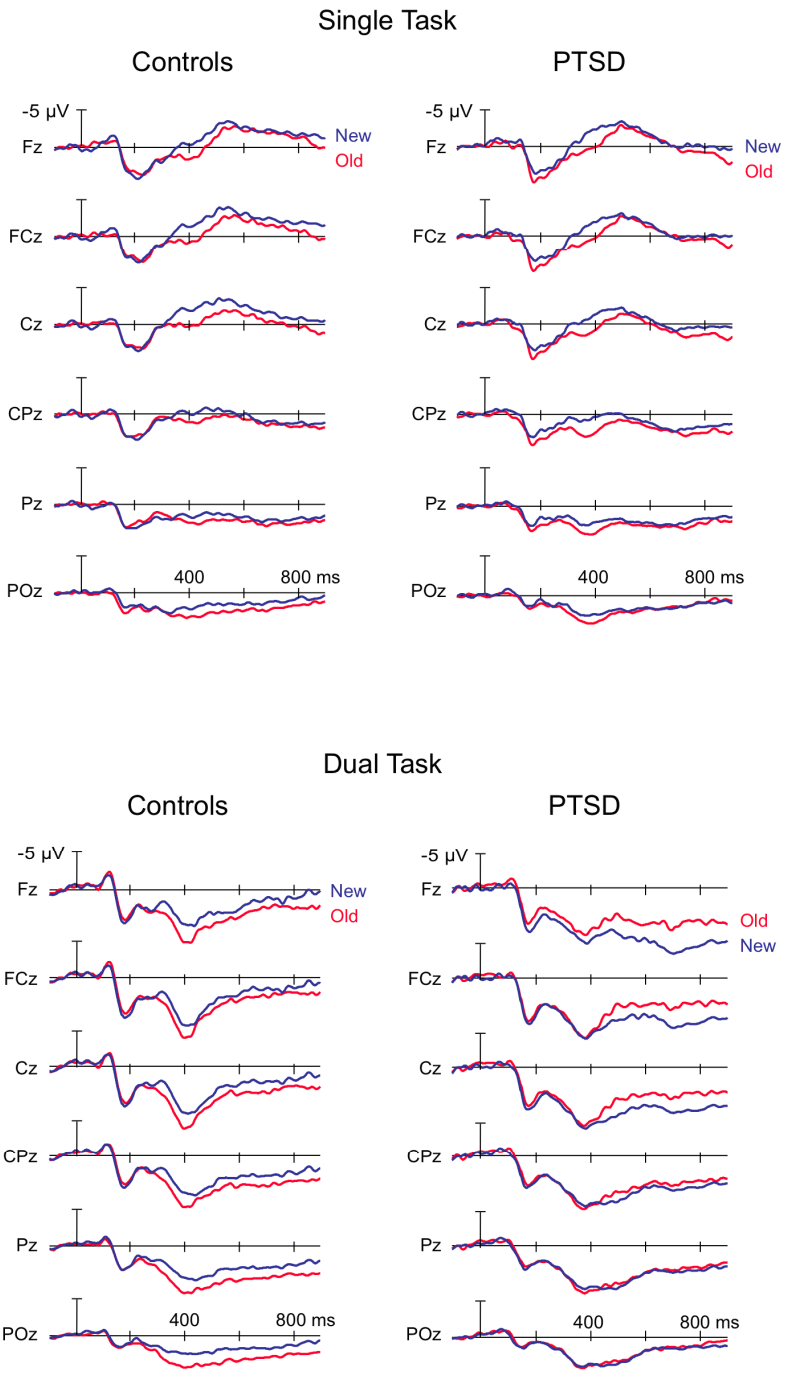

Accuracy
100
95
90
85
80
75
% Correct
*
Controls
Patients
Single Task
Dual Task

Figure 2.


Single Task
Controls
PTSD
-5 μV
Fz
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New
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Dual Task
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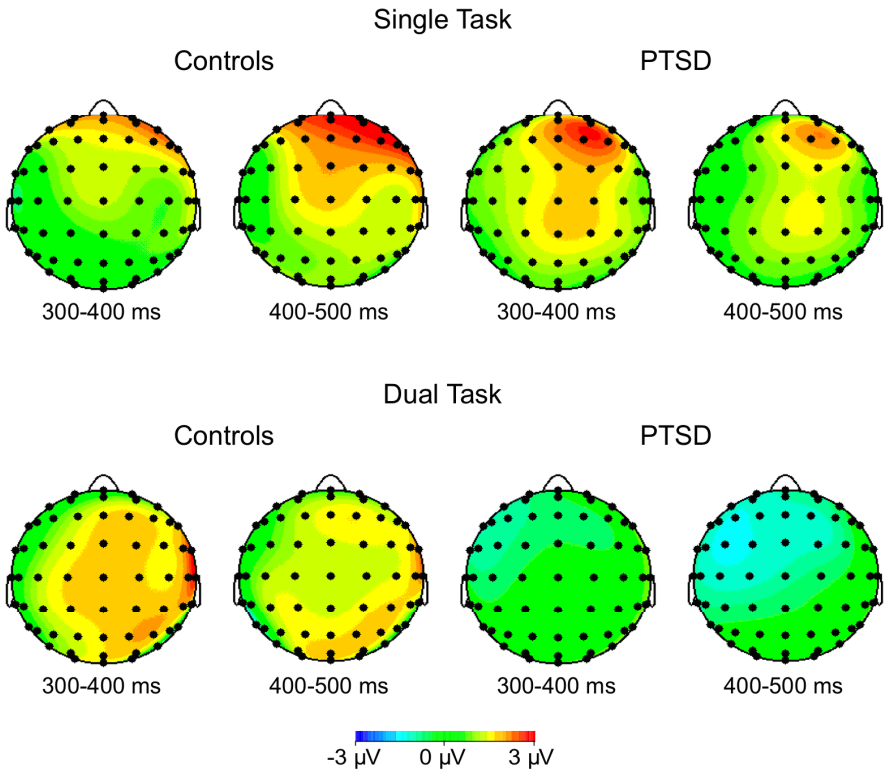
New
Old
400
800 ms

Figure 3.


Single Task
Controls
PTSD
300-400 ms
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Dual Task
Controls
PTSD
300-400 ms
400-500 ms
300-400 ms
400-500 ms
-3 μV
0 μV
3 μV

# Response Inhibition and the Inferior Frontal Gyrus: Are There Task Differences in Lateralization?

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An influential theory holds that motor response inhibition is strongly lateralized to the right prefrontal cortex (PFC), based on evidence from neuroimaging and neuropsychology (Aron et al., 2004). The human lesion evidence is based entirely on results from the Stop-Signal RT task, where patients with lesions in right IFG, but not left IFG, were impaired in SSRT. However, we recently reported that 12 patients with focal damage in left IFG and insula showed response inhibition deficits in the Go/NoGo task, particularly when responses were more prepotent (90% vs. 50% Go probability; Swick et al., 2008). This raises the possibility that the two tasks might be tapping different elements of response inhibition. Here, we present new data from patients with R PFC lesions in GNG. Three of the four had increased numbers of missed Go trials, suggesting a deficit in sustained attention rather than response inhibition. This pattern was exaggerated in the patient with the most extensive RIFG damage. This patient also had increased NoGo errors in the 50/50 condition but not the 90/10 condition, which does not suggest impairment in response inhibition alone. We also conducted separate meta-analyses of neuroimaging results from GNG (620 foci) and SSRT (130 foci) using the Activation Likelihood Estimation method (Laird et al., 2005). Activations in SSRT were actually more bilaterally represented in PFC and insula than in GNG. Combined, these results demonstrate the importance of obtaining behavioral data from both GNG and SSRT in the same groups of patients and the same fMRI experiments.

## Human Brain Mapping 2009

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# Lateralization of Response Inhibition in the Inferior Frontal Gyrus: It's Not Always Right

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**Introduction:** An influential theory holds that motor response inhibition is strongly lateralized to the right prefrontal cortex (PFC), based on evidence from neuroimaging and neuropsychology (Aron et al., 2004). The human lesion evidence is based entirely on results from the Stop-Signal Reaction Time task (SSRT), where patients with lesions in the right inferior frontal gyrus (IFG), but not the left IFG, were impaired in SSRT (Aron et al., 2003). However, we recently reported that 12 patients with focal damage in the left IFG and insula showed response inhibition deficits in the Go/NoGo task (GNG), particularly when responses were more prepotent (90% vs. 50% Go probability; Swick et al., 2008). This raises the possibility that the two tasks might be tapping different elements of response inhibition, each with distinct neuroanatomical and psychopharmacological correlates (Eagle et al., 2008). In fact, a new model of response inhibition (Schachar et al., 2007) distinguishes between action restraint – inhibition of a motor response before the response has been started (GNG), and action cancellation – inhibition of a motor response during its execution (SSRT). Several meta-analyses of response inhibition tasks have been published (e.g., Buchsbaum et al., 2005; Nee et al., 2007; Simmonds et al., 2008), but none of these have looked at GNG and SSRT separately.

**Methods:** To further explore whether these different subtypes of response inhibition can be dissociated neuroanatomically, we conducted separate quantitative meta-analyses of functional imaging data from GNG and SSRT using the Activation Likelihood Estimation (ALE) method (Laird et al., 2005). The BrainMap database and PubMed searches identified 39 relevant papers reporting activations in response inhibition tasks: 620 foci, 45 experiments from GNG and 130 foci, 11 experiments from SSRT.

**Results:** The maps produced by the ALE meta-analyses identified the regions of activation common to successful response inhibition in the Go/NoGo task (Fig. 1) and the Stop-Signal RT task (Fig. 2). Surprisingly, activations in SSRT were more bilaterally represented in the PFC and insula than in GNG, which showed a strong right lateralization. For GNG, major clusters were centered in the right middle frontal gyrus (BA 9, 46) and insular cortex (BA 13), the superior frontal gyrus (medial BA 6), and the right inferior parietal lobule/precuneus (BA 40, 7). Also notable is a large cluster in the left putamen/claustrum/insula, which overlaps with the insular region damaged in our left IFG patient study (Swick et al., 2008). For SSRT, major clusters were centered in the right insula (BA 13) and globus pallidus, the left insula and putamen, and the superior frontal gyrus (medial BA 6).

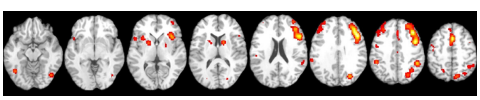
Fig. 1 - ALE map from GNG tasks.

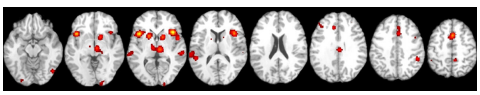
Fig. 2 - ALE map from SSRT tasks.

**Conclusions:** These findings are consistent with the notion that there are multiple elements of response inhibition that are not all captured by a single task. It will be important to obtain data from both GNG and SSRT in the same fMRI experiments and the same groups of patients to fully characterize the neural substrates of response inhibition.

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# ATTENTIONAL BIAS AND RESPONSE INHIBITION IN VETERANS WITH POST-TRAUMATIC STRESS DISORDER AND TRAUMATIC BRAIN INJURY

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VA Northern California Health Care System

**Background and Objectives:** Combat veterans who have sustained a traumatic brain injury (TBI) can show impairments in behavioral and cognitive control and increases in impulsivity. In addition, many with mild TBI also will have post-traumatic stress disorder (PTSD). To improve diagnostic capabilities and better define treatment alternatives, it is important to determine the unique (and shared) contributions of each disorder to cognitive and emotional deficits.

**Methodology:** Two computerized cognitive tests were administered to 15 male veterans (mean age 32.8 years) with PTSD and/or mild TBI (9 TBI + PTSD, 5 PTSD only, 1 TBI only). Experiment 1 was an emotional Stroop task with combat-related words, in which participants named the font color of words presented on the screen while ignoring the words themselves. The words were presented in blocks of negative emotional words, positive emotional words, combat-related words, and appropriately matched neutral words. The metrics of interest were reaction times (RTs) for naming the color of combat words relative to neutral words, as the former are thought to divert attention away from the primary task in veterans with PTSD. Experiment 2 was a Go/NoGo task that measures the ability to inhibit an inappropriate response. The difficulty of the task was manipulated by altering the probability of "Go" trials relative to "NoGo" trials (i.e., 50% Go trials vs. 90% Go trials), with 50% NoGo vs. 10% NoGo, respectively. Performance measures from the patient group (error rates and RTs) were compared to those from age-matched civilian control groups.

**Results:** In Experiment 1, there was a clear emotional Stroop effect (slowing of RTs) for combat-related words in veterans with PTSD (176 msec), but not in controls (8 msec). The size of the Stroop effect and scores on the PTSD Checklist-Military were not correlated. The patients also showed significantly impaired response inhibition in Experiment 2, committing more errors than controls in both conditions. Furthermore, "Go" probability interacted with the group, such that the patients were impaired to a greater extent on the difficult condition, indicative of an impulsive response style. Although the subgroup numbers are still small, there was no suggestion that veterans with TBI + PTSD differed from veterans with PTSD only on either task. Furthermore, self-rated impulsivity on the Barratt Impulsiveness Scale (BIS) did not correlate with performance. However, total BIS scores for 11 of 15 patients placed them in the high or high-normal impulsive range, so most were able to gauge their level of impulsivity in an accurate manner.

**Conclusions:** The emotional Stroop test shows promise as an objective behavioral measure that may be able to distinguish between combat veterans with a PTSD diagnosis and those without. However, these results should be interpreted with caution until a demographically matched group of military controls is tested. In addition, the present group of OIF/OEF veterans had a substantial deficit in motor response inhibition, which can have implications for daily life.

**Impact Statement:** Increased levels of impulsivity and a decreased ability to filter out distracting and emotionally intrusive information can negatively impact social and occupational functioning. In the future, computerized training interventions that target emotional and cognitive control skills may assist these OEF/OIF veterans in returning to their previous levels of productivity.

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When the going gets tough, attention starts going

Nikki Pratt1, Adrian Willoughby2, Diane Swick1,3;1VA Northern California Health Care System, 2University of Birmingham, UK, 3University of California, Davis

Previous research suggests that the prefrontal cortex is important in both directing attention to relevant stimuli and maintaining information in working memory (Corbetta & Shulman, 2002). Few studies, however, have reported the effect of working memory load on attention via top-down cortical connections. The following study addresses the extent to which working memory load influences early (P1) and late (P300) attentional ERP components using a dual task paradigm. Participants were presented with an arrow flanker task alone (single task condition) or along with a Sternberg memory task (dual task condition). In the flanker task, participants responded to the direction of a central arrow surrounded by congruent or incongruent arrows. In the dual task condition, participants were presented with a Sternberg task comprised of either 4 or 7 consonants to remember prior to a short block of 8 flanker trials. Behavioral and electrophysiological responses were analyzed in response to the flanker trials and compared across the single and dual task conditions. Participants were slower and less accurate on incongruent versus congruent trials, regardless of the load on working memory. Furthermore, both load conditions reduced accuracy on incongruent flanker trials. Likewise, amplitudes for the P1 and P300 components were diminished to flanker trials when the Sternberg memory set was introduced. This suggests that working memory influences attentional resources in the brain regardless of response conflict. Importantly, the P1 finding indicates that top-down attentional control over early visual processing is diminished by increasing demands in working memory.

Session Assignment: First Choice = EXECUTIVE PROCESSES: Goal maintenance & switching, Second Choice = ATTENTION: Nonspatial

Cognitive Neuroscience Society Meeting, Apr 2011.

**Attentional bias for trauma-related words: Exaggerated emotional Stroop effect in Iraq and Afghanistan war veterans with PTSD and TBI**

Victoria Ashley, Diane Swick, Nikki Pratt, Jary Larsen and Timothy Justus

The emotional Stroop effect and has been studied extensively in those with anxiety disorders and depression (Williams et al., 1996), but less so in the context of combat-related post-traumatic stress disorder (PTSD) (Constans et al., 2004). Intrusive cognitive activity, increased attentional biases and hypervigilance for threat cues are typically seen in PTSD, but only for threat-related information rather than general emotional information. To examine whether combat-related words would elicit unique interference in US veterans with PTSD and/or mild traumatic brain injury (TBI) received during Operation Iraqi Freedom (OIF) or Operation Enduring Freedom (OEF), we measured accuracy and reaction times to color naming on an emotional Stroop task and administered the Beck Depression Inventory (BDI) and the PTSD Checklist (PCL). Groups were 20 PTSD/TBI veterans (mean: 32.0 yrs), 20 military controls (mean: 33.5 yrs), and 20 civilian controls (mean: 32.1 yrs). The emotional Stroop task used 5 different blocks of 84 unique words each: neutral, positive, negative, combat-related, and combat-matched neutral, in a Latin-square counterbalanced order. Results showed a clear emotional Stroop effect (slowing of RTs) for combat-related words in PTSD/TBI veterans (115 msec), but not in military (21 msec) or civilian controls (33 msec), and more errors to combat-related words in PTSD/TBI veterans than controls. Stroop RTs and scores on the PCL and BDI were also correlated. The emotional Stroop test may show promise as an objective behavioral measure to distinguish between combat veterans with a PTSD diagnosis and those without.

Cognitive Neuroscience Society Meeting, Apr 2011.

**Performance on Go/NoGo and Stop-Signal Response Inhibition Tasks Is Not Correlated**

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Two major tasks are used to assess response inhibition, an essential executive control function. In the Go/NoGo (GNG) task, a motor response is made to one stimulus class and withheld to another. In the Stop-Signal Task (SST), responses are made on every trial unless a stop signal is presented. Although these two tasks are often treated interchangeably, it is unclear whether they tap the same cognitive processes and neural substrates. A previous meta-analysis of the neuroimaging literature suggested they have both overlapping and distinct neural substrates, the latter reflected by differential recruitment of two cognitive control networks (Swick et al., 2010). Here, we present data from 49 subjects tested in standard versions of GNG and SST. We wished to see whether performance on the two tasks was correlated. Participants included controls (n=25) and patients with TBI and/or PTSD (n=17) or focal frontal lesions (n=7). In GNG, subjects responded to all letters except for X, the NoGo stimulus occurring on 50% or 10% of trials. In SST, subjects responded to all R or L arrows unless they heard the stop signal tone on 25% of the trials. Stop signal delay was adjusted using a 4-staircase procedure designed to produce 50% error rate. Stopping ability was measured by stop signal reaction time (SSRT) and compared to GNG error rates. Results demonstrated that within and across groups, NoGo errors were not correlated with SSRT. Combined with the meta-analysis results, these data suggest GNG and SST are not identical measures of response inhibition.




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# Poster Abstract

**Poster I4**, Tuesday, April 3, 3:00 – 5:00 pm, 4th Floor Exhibit Hall

## Impaired identification of facial expressions of fear in Iraq war veterans with PTSD and mTBI

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Studies suggest that patients with post-traumatic stress disorder (PTSD) process emotional facial expressions differently then healthy individuals; PTSD patients display exaggerated amygdala and diminished prefrontal cortex responses to fearful facial expressions. A recent study also found specific accuracy impairments and decreased sensitivity in recognizing expressions of fear and sadness in war veterans with PTSD (Poljac et al., 2011). To assess the role of PTSD in facial expression recognition, we showed pictures of faces to Iraq war veterans with PTSD and mild traumatic brain injury (mTBI), and to healthy age-matched military controls, and asked them to identify the expressions. A total of 140 faces (Ekman & Friesen, 1976) were presented in black and white, one at a time, in pseudo-randomized order. Faces had one of six basic expressions (happy, angry, fear, surprise sad, disgust) or neutral, with half of the expressions at 100% full intensity and the other half at 50% intensity made by morphing expressions with neutral (Calder, et al., 1996). Preliminary results suggest that, like Poljac et al. (2011), PTSD patients show impaired accuracy at identifying 50% intensity fear faces, relative to military controls ($p<.05$; Accuracy: patients=38%, controls=51%) and display a trend for impaired accuracy for full intensity fear faces ($p<.06$). PTSD patients also show a trend for misidentifying fear as surprise ($p<.1$). Our study did not find impairments on expressions of sadness, but is consistent with a growing body of research indicating altered processing of fearful facial expressions in PTSD (Poljac et al., 2011; Beevers et al., 2011).

Topic Area: EMOTION & SOCIAL: Emotion-cognition interactions

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